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ADVISORY COMMITTEE MEETING NO. 50

OPEN SESSION

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C O N T E N T S

AGENDA ITEM	PAGE
QUESTIONS REGARDING CLINICAL TRIALS FOR BIOLOGIC IMMUNOMODULATORY PRODUCTS FOR PSORIASIS	
Call to Order and Welcome	3
Conflict of Interest Statement	3
Open Public Hearing	6
Pathopshysiology of Psoriasis	36
Overview and Summary of Adverse Events	47
Committee Discussion	48
TINEA CAPITA CLINICAL TRIALS ISSUES	
Call to Order: Welcome and Information	76
Conflict of Interest Statement	78
Introductory Remarks	79
Open Public Hearing	80
Dr. Ilona Frieden - "Tinea Capitis: An Emerging Public Health Issue"	84
Dr. Sheila Fallon-Friedlander - "Clinical Presentations of Tinea Capitis"	101
Dr. Dennis Babel - "Mycology of Tinea Capitis"	116
Dr. Boni Elewski - "Current Therapies for Tinea Capitis"	132
Dr. Paul Honig - "Topical Adjunctive Therapy to Reduce Contagion"	147
Committee Discussion	155
Adjourn	194

P R O C E E D I N G S

DR. McGUIRE: Let me remind you that you are at the Dermatologic and Ophthalmic Drugs Committee Number 50. We're going into our open public hearing, but before we do that, there's a conflict of interest statement to be read.

MS. RILEY: Good morning. I have two conflict of interest statements here. The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the Committee participants, it has been determined that all interests and firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions.

Since the issues to be discussed by the Committee at this meeting will not have a unique impact on any particular firm or product, but rather may have widespread implications with respect to an entire class of products, in accordance with 18 U.S. Code 208(b), each participant has been granted a waiver which permits them to participate in today's discussions. A copy of these waiver statements may be obtained by submitting a written request to the agency's

Freedom of Information office, Room 12A-30 of the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record. With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

And the second one is from the Center for Biologics and it's in accordance with 18 U.S. Code 208(b)(3), Dr. Gerald Krueger has been granted a general matters waiver which permits him to participate in the open scientific discussion of clinical trial design issues for systemic immunomodulatory biological products intended for the treatment of psoriasis.

Thank you.

DR. McGUIRE: I would like for the members of the agency and the Advisory Committee to identify yourselves. We'll begin with Dr. Siegel.

DR. SIEGEL: Hi. I'm Jay Siegal, Office of Therapeutics at the Center for Biologics, FDA.

DR. WEISS: Karen Weiss, Division of Clinical

Trials, Center for Biologics.

DR. SCHWIETERMAN: Bill Schwieterman, Division of Clinical Trials, Center for Biologics.

DR. MARZELLA: Louis Marzella, Division of Clinical Trials, Center for Biologics.

DR. WILKIN: Jonathan Wilkin, Division of Dermatologic and Dental Drug Products, Center for Drugs.

DR. KO: Hon-Sum Ko, Medical Officer, Division of Dermatologic and Dental Drug Products, Center for Drug Evaluation and Research.

DR. SIMMONS-O'BRIEN: Eva Simmons-O'Brien, Departments of Dermatology and Internal Medicine, Johns Hopkins, Baltimore, Maryland.

DR. KILPATRICK: Jim Kilpatrick, biostatistician from the Medical College of Virginia, Virginia Commonwealth University.

MS. RILEY: Tracy Riley. I'm the Executive Secretary of the Committee.

DR. McGUIRE: I'm Joe McGuire, Pediatrics and Dermatology, Stanford.

MS. GOLDBERG: I'm Jackie Goldberg. I'm the consumer representative and I run the Health Sciences IRB at the University of Missouri.

DR. TSCHEN: Eduardo Tschen, Department of Dermatology, University of New Mexico.

DR. MINDEL: Joel Mindel, Departments of Ophthalmology and Pharmacology, Mt. Sinai Medical Center, New York.

DR. DUVIC: Madeleine Duvic, Dermatology and Internal Medicine, MD Anderson, Houston, Texas.

DR. MILLER: Fred Miller, Dermatology, Geisinger Medical Center, Pennsylvania.

DR. ROSENBERG: Bill Rosenberg, Dermatology and Preventive Medicine Department, University of Tennessee College of Medicine, in Memphis.

DR. DiGIOVANNA: John DiGiovanna, Department of Dermatology, Brown University, and the National Institutes of Health.

DR. McGUIRE: We'll go to the open public hearing and the first person to speak is Dr. James Krueger from Rockefeller.

DR. J. KRUEGER: First, I'd like to thank Chairman McGuire for the way in which he has been running this meeting and for allowing for a reasonable amount of public comment and input into the discussion that had occurred for questions among Committee members yesterday. I hope he will continue that today.

I want to address several issues which I think have been in the background of trial designs for biologics over the last several months which concern me as an academic

physician. And I am commenting here and representing myself and my own views on this. I do not have any corporate interest that puts me in conflict in these.

The first concern that I have heard stated is that psoriasis is essentially a cosmetic disease and that the risk-to-benefit ratio simply doesn't favor exposing patients to potentially toxic agents for management of this disease. I have three patients I want to show you pictures of where this disease has really wrecked their lives and to tell you this is what we face as academic physicians in trying to deal with this disease.

This is a 20-year-old woman. You can see she has psoriasis over her whole body. She had psoriasis onset at age 12 and, since age 12, has been through the therapy mill with methotrexate, PUVA, combinations of PUVA and methotrexate, UVB, cyclosporine, and she has not had retinoids because they have only been recently introduced for women of child-bearing potential. But, essentially, she has been through the whole mill. She can't function when her skin is like this and if she is not on very highly active therapy, she can't function.

The second is this 18-year-old who has had psoriasis for only two years, and whole skin looks like this, inflamed areas, which she also cannot function when her skin is in this state and requires continued therapy to

maintain a functional state.

The third patient is this 35-year-old computer programmer who has had psoriasis since his early 20s. He had clear skin six weeks before this because he was on cyclosporine, but cyclosporie was stopped. And I think you can appreciate here we have a highly inflammatory, eruptive mess, and needless to say, when his skin looks like this, he can't function as a computer programmer because he's too focused on the pain and the itching of his skin.

All right, so we have a group of patients that we call moderate to severe that need to be managed constantly by therapy and often have disease onset in their teenage years to early 20s and we're managing them over a lifetime. What we use to manage them is, in part, the FDA-approved agents--UVB, PUVA, acitretin, cyclosporine, methotrexate, each of which has considerable toxicity such that, for instance, PUVA induces skin cancers with reasonable certainty above a certain number of treatments, and methotrexate can certainly lead to cirrhosis.

The intrinsic toxicity of these agents is acknowledged in this rotational therapy scheme where we try to minimize damage to any one organ by rotating through agents that have differing kinds of toxicities. However, for many of the patients that are really bad, we run out of the agents on this rotational therapy scheme because they

either fail to respond or they develop toxicities, and then we need something else.

Something else takes people like me down the road of even more serious drugs, and one of the things that I pull out of a hat is Thioguanine, which is a cancer chemotherapy antimetabolite that is used to treat chronic lymphoma and works extraordinarily well in treating psoriasis in severe patients when their bone marrows will tolerate the drug.

However, it's within this realm of the severe patients when we leave the approved therapies that we potentially have serious toxicity that may result from what we do in trying to make these patients functional. And so I don't think you can consider what we're doing here as the treatment of a benign disease.

The second point that I want to make is for a long time we've been in a therapeutic hole because we didn't understand the pathogenesis of this disease and therefore had no idea about how to go about developing new therapies. And with the realization that psoriasis is fundamentally an immune process, or at least that's a hypothesis that we can follow and test, we are able to now rationally bring in new agents that have been engineered to interfere with specific kinds of immune reactions and at least ask whether our hypothesis is right about this disease, and if it is to

begin to develop, hopefully, a wider range of treatment options for the more severe patients.

Now, one thing that I want to point out here is we're in biologics. One of the raison d'etres behind adding biologics is the belief that we understand this pathogenic scheme. But there is a cellular pathway here in which we activate cells; they proliferate and expand clones and then infiltrate skin. And there are a variety of biological molecules which interfere with different steps in this process.

If we add a molecule that interferes out here, we may see clinical benefits sooner than if we add an agent that interferes with this first step and requires time for the cells here to die by spontaneous mechanisms. Thus, depending on what agent we add in, we may need time to establish whether, in fact, it works. And I'm concerned about certain of the study designs that now go forward because they're essentially painting us into a box where we can't do this kind of testing.

I think the time frame for what is required to test agents is suggested to some extent by cyclosporine. We recognize that it's one of the most effective agents that we have. This is a patient treated with cyclosporine for two months at the point the picture is taken. However, in population trials, I think you really need six weeks to

eight weeks of treatment with this highly active agent in order to establish whether there are significant clinical responses to it. And therefore if you had done a single few does of cyclosporine, you probably wouldn't have seen any benefit and you would have dismissed it as an agent. That may happen now with certain trial designs that are suggested at least in early safety studies.

Secondly, there is the idea perhaps that any agent that interacts with a T cell may produce untoward toxicity by activating that T cell. Alice Gottlieb and I have been involved in a physician-sponsored IND in which we have been looking at the effects of humanized antibodies to CD25 in this disease. I don't want to tell you anything about the efficacy outcomes, but I want to address the safety of this study.

This is a study where we initially gave 2 milligrams per kilogram of an agent for a T cell molecule that is overexpressed in psoriasis and might therefore lead cells to be more sensitive to it. In fact, by giving multiple doses in milligram quantities of this antibody over a period of two to three months, we have seen no significant drug-related toxicity in 19 patients. And I think this established at least one principle that the right antibody interacting with a T cell can be safe, and I would urge a careful consideration of agent-by-agent mechanism in terms

of how we construct both trials and the safety structure for going forward.

And my final two comments are without slides. First, I would like to applaud Dr. Wilkin's position yesterday in which he said it is the position of the agency not to interfere with the practice of medicine. And I would like to say from an academic physician's standpoint I view that there are two responsibilities. The first is to advance treatment for disease and to provide treatment for my patients. However, the academic responsibility is one where I think we need to ferret out and understand the pathogenesis of disease and use that information to better the needs of our patients.

We're at an unusual junction with the biologics in the practice of medicine, in that what we can learn scientifically from the considered use of these agents begins to approach the kind of information that is had in animal models, the gene knockouts, in order to understand what molecules are important and what are not, and to do hypothesis testing for schemes of this disease and other related diseases.

Now, we can't do a gene knockout in a person, but we can add specific antagonists of specific molecule and ask what are the downstream effects, both on the disease and on molecular pathways that we think are important. Our ability

to do this is through the kind of biologics that now exist for the most part to some extent with drugs. I would hope that you would be sympathetic to the need of physicians in this country to be able to do the kind of investigative medicine that is necessary to take this path. We can't have a treatment situation which precludes work being done in the United States.

The second point I want to make then addresses study design. I know we're going to be talking about it this morning, but the idea of using single doses of agents in washed-out patients who are followed for long periods of time in escalation of dose by cohort simply doesn't work well for these patients that are moderate to severe because we lead them to crisis. They end up in the kind of state that I showed you here. In fact, they may be very difficult to get back into the therapeutic box, and that is we may deal with them in crisis for months after their skin has become very, very inflammed.

I'm in favor of thinking about different kinds of trial designs. At least in part, one could consider where, for instance, cytokine release is a concern to do dose escalation by patient with relatively short cycle times because the toxicity that you're looking for will be evident within a day or two of a dose. It doesn't make sense, then, to treat a group of six, ten patients with that over a

period of a month, have people washed out and then think about where do you find another group to dose-escalate.

In fact, the question about what level of drug induces cytokine release, if, in fact, it happens, can be established within a patient, I think, with reasonable safety. And there may be other designs such as this that would permit us to have a workable scheme. Another that was suggested yesterday is to segregate safety from efficacy studies in early phases and simply be able to look for cytokine release in patients that are on appropriate other agents to have some kind of control over their disease. Clearly, something like cyclosporine wouldn't make sense because you might inhibit cytokine transcription and response to activating agents. But there are a variety of other things that we have that would be.

So I would like to urge thought for all of us going forward, and hopefully some temperance on the part of our advisers in terms of constructing unworkable, and I think perhaps medically unethical kinds of study designs that we're going to be forced to follow.

Thank you.

DR. McGUIRE: Thank you, Dr. Krueger. You made your points very clearly until you got to the point where we were intemperate, but we can deal with that in questions.

[Laughter.]

DR. J. KRUEGER: Actually, my comments are addressed mostly to one side of the table and not the other, but perhaps I'm getting further and further into--

DR. McGUIRE: I think so. This is the time to stop.

Dr. Gottlieb?

Since we're running against the clock, what I'd like to do is to have all the people speak and then if there are questions from the Advisory Committee or from other members of the audience, we can have them then.

DR. GOTTLIEB: I'm Alice Gottlieb and I'm representing myself, and one of the reasons that I paid personally to come here is to avoid this situation which says the doctor is telling his patients, "unfortunately, there's no cure; there's not even a race for a cure." And I'm worried that this is where we're headed toward if things keep as they're going.

I'm going to reiterate some of the things that Jim has said, but I actually think they need to be reiterated. As I say, I think it's appropriate to be concerned with safety. However, studies that have no expected benefit are not worth any risk at all, and I personally feel that it is unethical to have long washouts with no-effect doses for months, with follow-up for months. And I think the solution, as was stated yesterday, if one is going to use

this kind of design, is to do it in less severe patients.

I think it's even more unethical to have a placebo in this setting, and from what I heard yesterday, and we're going to discuss it today, it's not actually required to have to have a placebo in these studies. And I think that it's just unconscionable to tell patients to have washouts, months of placebo, and they usually have a 1-to-4, 1-to-6 chance of getting it, and then for some follow-up period.

And I think that if one is going to have this kind of design, one at least has to put them on something, even if it's a topical corticosteroid, and you can have a dummy vehicle, you know, however you want to do it. But you can't put them on nothing. I mean, I think that it is highly unethical and I see it time and time again, and we're told from the sponsors that the FDA makes them do it. And now I hear that the FDA says you don't have to do it. So I think that that's something that should be addressed by the Advisory Committee.

I do not think that the proposal to have patients on some stable regime is going to be practical because if they're moderate to severe patients, that stable regime might be methotrexate, PUVA, or cyclosporine, and I think those would confound your safety studies. So I don't think that's a very practical way to do it.

I also wanted to hear how this Committee thinks of

the cytokine release syndrome because I've heard it mentioned time and time again, but I have not seen any proof that indeed that does happen. So it would be interesting to discuss whether indeed you do demonstrate cytokine release when you treat these patients and have these adverse events. And, B, aseptic meningitis; what cytokine gives you aseptic meningitis, which is one of the major effects you're seeing? I know that because one of them is my patient.

So if it is indeed aseptic meningitis, have you demonstrated the mechanism by which that occurs before one hypothesizes and it goes on and on? It is said so many times that people believe it whether there's proof or not for it and I think that it still needs to be addressed. The FDA has sent a safety pamphlet around which talks about aseptic meningitis in the setting of giving polyclonal immunoglobulin. That's an FDA publication that I received. And, again, if polyclonal immunoglobulin can do it, can give you aseptic meningitis, is that based on cytokine release syndrome? Is that FC-mediated? And so I think that some science needs to be done before major decisions are made. This is a publication from the FDA that I got.

And those are my comments. Thank you.

DR. McGUIRE: Alice, thanks very much. After we finish with the public hearing, then we'll have the agency respond to your specific and pointed questions.

The next speaker is Dr. Todd Plott, from Schering-Plough.

DR. PLOTT: Thank you for the opportunity to speak. If you would push that up just a little bit, I represent the Schering-Plough Research Institute and I'd like to address the comments and, specifically anticipating the questions that the Committee may have to answer, focus on the design of clinical trials for these agents in psoriatic patients.

I think that in anticipating a clinical program that's going to demonstrate safety and efficacy for one of these agents that we need to focus on three clinical objectives from a pharmaceutical standpoint. We first need to identify the tolerable dose. What is the dosing range that we can administrate safely to these patients? Then we need to look at dose justification. How are we going to justify the dose that we're finally going to recommend? And then, third, to demonstrate safety and efficacy in the population that we intend to treat.

In these early clinical studies safety, I think, is the primary concern. And in the early trials that we've mainly been focused on so far, we're concerned about safety. We need to determine what is the most tolerable dose, and in order to do that we believe that we need small numbers of patients. And, of course, there's been some debate about

what the severity of the patients should be, and I wish just to leave that as an issue to be debated, not to provide comment, except that this decision needs to be based on data and it needs to be based on what's known about the agent and considerations made on a case-by-case basis.

Once I think that safety is somewhat understood, moving on to justification of the dose, there's a balance in determining what this dose justification needs to be. It's sometimes referred to as a risk/benefit. It's a balance between what is safe and what is efficacious, and to determine this I think that we can use probably patients that have less severe--clearly, in this determination, patients who are less severe can be evaluated. We need to be able to evaluate larger numbers of patients than what we've done before in determining a tolerable dose. And we probably need to treat for longer periods of time, and certainly we need to be following patients for longer periods of time than what we did in order to find a tolerable dose.

Once we've looked at dose justification, going on to efficacy, I believe that primary endpoints should be clinically-based. There have been comments about using microscopic or histologic evaluations. These are fine as secondary endpoints, but when patients come to the office, they want to see that their psoriasis is better. Physicians

using these agents want to do tests which are not so complicated. And so patients and physicians both want to see that the psoriasis is being cleared and the best to do that is to have endpoints that are clinically-based. This is also, I think, is important for labeling. You need to be able to tell patients what they can expect from their therapy, and we believe that using target lesions in clinical trial designs can be helpful in addressing the efficacy of the product.

Also, other issues that need to be looked at possibly are onset of action, and then something I would call duration of response rather than remission, as you considered yesterday, just what is the duration of the response after the therapy has been discontinued.

In exploring the safety, it's important that we conduct these trials in the population that's likely to receive this product. Even though this is a biologic--it has been tested in very severe patients--we know that it quite likely could go on to less severe patients. And we should know about the safety in those populations, so we should be testing in less severe patients or in a realistic patient base.

And we should be looking at issues really on a case-by-case basis. Each of these biologic agents could have unique toxicities which could cause immunosuppression

during or after therapy, and then also there could be related unique adverse events that could be created on a case-by-case basis again.

So, in conclusion, we believe that it's very important to proceed cautiously at first until safety is understood; once some safety has been established, proceeding with larger trials in less severe patients for dose justification and safety and efficacy, and that there must be data-driven, fact-driven decisions made on a case-by-case basis in moving through the development of these individual agents.

Thank you.

DR. McGUIRE: Thank you, Dr. Plott.

Bill Gannett?

[No response.]

DR. McGUIRE: Bill Gannett is down for the open session. Is he here?

[No response.]

DR. McGUIRE: Okay, then let's have a few questions directed toward the first three speakers.

Dr. Weiss?

DR. WEISS: Yes, I just have a question for Dr. Krueger. The patients that you showed us in the beginning with the severe disease--I just need to get a sense of what kinds of therapies those patients are on. You mentioned

that some of them have exhausted all their possibilities. We know that cyclosporine is something that is not--some of these agents cannot be used for particularly long term.

So when you show us a picture of a patient like that and tell us how affected they are by the disease, which we can all appreciate, and the fact that there's a desperate need for new therapies, what are those patients, when they would come to you or maybe be coming to be participating in a clinical trial--what would they be on right now?

DR. J. KRUEGER: They may be on some continued ultraviolet therapy. The first woman I showed you had been on some combination of methotrexate and phototherapy or PUVA, with only partial control of disease, and be treated with Dioguanine with fairly good inmprovement, but not a very durable period of benefit.

My opinion is they might be suitable candidates for PUVA, but I have major concern about taking a 20-year-old and starting them on PUVA, even though they're this bad, because I think we are painting ourselves into a box of squamous cell carcinoma 20 years from now. And, you know, that creates certain problems with the biologics going forward because I think we want to also consider the safety of the carcinogenicity versus immunosuppression. They are very, very difficult to treat in that we've got to try and find something that improves them to the point they can

function.

DR. WEISS: But I guess this goes to the question that we're going to be trying to pose to the Committee and that's been discussed somewhat yesterday as well with this issue of the washout, which obviously has raised a lot of concerns by people who are doing therapy in this area. But I was just trying to get a sense for, if a particular individual such as the examples that you gave were there in your office and would be considered for a trial, what would they be on that would be--if there was a requirement for a washout that would be--which things would have to be, quote, "washed out" because of concerns about synergistic toxicity and which ones would you feel would be appropriate to potentially use with some of these immunomodulatory therapies?

DR. J. KRUEGER: Well, I think cyclosporine presents mechanistic difficulties in looking for safety-related things that may be on the T cell activation side. I'll tell you how this kind of patient is workable in a clinical trial. If they're treated with intensive phototheraphy--that is, UVB--for the most part the skin will clear and they may have a period of several weeks to a couple of months where their skin is under some kind of reasonable control.

And the relapse from phototherapy is different

than coming off cyclosporine, in that often small plagues begin to come back and then the disease gradually expands over time, instead of an explosive onset of the disease, so that they're suitable to some extent for investigational therapies if we had an effective therapy or a reasonable plan for them during that post-phototherapy period when their skin is under some kind of reasonable control.

If, on the other hand, we give them a single agent at that point, they probably won't have therapeutic benefit. And follow them for another month or two; their skin is going to get back to this stage that you see here and that represents the difficulty in washing out. With something like cyclosporine withdrawal, they could explode so fast that would say unless you had a highly active agent that you were trying, they probably wouldn't be suitable.

DR. McGUIRE: Yes, Dr. Schwieterman.

DR. SCHWIETERMAN: There were a number of comments actually, and questions, addressed to the agency. I just thought I'd address several of them before we got into the open public--to the more general discussion.

I think we agree, actually, with many of the comments that both Dr. Krueger and Dr. Gottlieb made. There needs to be careful thought and consideration to the types of trial designs that are appropriate for these therapies. With regard specifically to the long-term benefits of

chronic therapy, I think we would also agree with that that many of the cytokines are likely to have more benefit when given as multiple doses rather than as single acute doses.

And there's definitely a need to consider the value of bioactivity parameters, pharmacodynamic parameters, after single doses with respect to how that might translate into more chronic benefits. I think what this Committee needs to discuss, however, is the safety and the appropriateness of either inter-patient dose escalation or either multiple doses as an initial therapeutic regimen for products that have not been demonstrated, or at least not adequately been demonstrated to have been safe in this particular patient population.

There are no blanket rules about this, but clearly there are considrations about the safety and problems associated with cumulative effects in the inter-patient dose escalations with many cytokines, and that, in fact, is one of the questions that we have here. Dr. Gottlieb mentioned some of the adverse events that have been ascribed, or at least talked about, and I just wanted to say that there is, in fact--it's not just theory; there are, in fact, reported adverse events with regard to cytokine release, and so forth. And it's something that clearly has not been worked out and we're continuing to look at it, but it's a real phenomenon.

DR. McGUIRE: Yes. I assume that's going to be part of Dr. Marzella's presentation.

DR. SCHWIETERMAN: Well, yes, it is, except only in the general sense and I was wanting to particularly respond to Dr. Gottlieb.

DR. McGUIRE: Other questions?

Bill Rosenberg?

DR. ROSENBERG: I have a question, but I wanted to comment on some of what we've heard. First of all, I think the agency and all of us should not allow this issue to be, in my opinion, muddied the use of the word "immunomodulation." We're being told we have immunomodulating drugs here. If you're driving a car, you can have speed-modifying agents, called the accelerator and the brake, and there are times for either.

But to allow this debate to be phrased in terms of its immune system functioning and we will modulate it, I think, misses a whole lot of points. My understanding--it's not my field, just what read--is that in the area of multiple sclerosis, the down-regulators are seen not to be working and the trial with interferon, which is up-regulators, I understand, looks so good that things are happening. I could be wrong about that. It seems to me that's what I had read in the Lancet.

But at any rate, there's a big difference between

brakes and accelerators, and I think as a minimum the agency ought to ask the sponsors what they think they're doing, which brings us to what Dr. Krueger said about ferreting out the pathogenesis of disease. He referred to psoriasis as an immune process, with which I think all of us would agree now, and then he stopped there.

The question is the immune process. The body defense against syphillis is an immune process, as is presumably autoimmune disease, and interferon and immunoglobulin GIV are things which, you know, shouldn't be lumped in the same, in my opinion, cup with agents which throw monkey wrenches into the body's immune system. The immune system is second only to the nervous system in its complexity and just to toss things in there and say we're modulating it, without knowing whether you're trying to go up or down or sideways, is not going to lead us anywhere.

And, of course, the agency has troubles with--you know, there's a drug that when you're tired picks you up and when you're tense calms you down, and the agency has a lot of trouble with nicotine. So I think it's going to be equally if we don't think about agents here that way. And we're back then to the theoretical concept of whether the immune system is acting inappropriately or appropriate. If it's inappropriate, then I think we have to do this sort of thing, certainly, in the short run. If it's appropriate,

then the hazards of these drugs come down the long road. They aren't seen in the first week or the first year, maybe, but only later on when perhaps people start to die.

We know about what Fauer [ph] solution--a great drug for psoriasis, as they used to say, if either the doctor or the patient is over 65, because of the troubles that came 20 years later. And because this field--things that seemed like a good idea a year-and-a-half ago, like other fields, are not necessarily so, I would again say that the work of Torag at Dallas Southwestern, and then what has followed from that where HLA-B27, the first HLA association with human disease, the one that everyone followed, the most striking associations, antigen presentation, et cetera, et cetera--when you get it really down and push it into the rat, and so forth, it doesn't work in the germ-free state.

And so there are microbes that are there driving that and we just have to think about that when we're talking about down-regulating, and we shouldn't allow ourselves to fall into the idea of just saying we're modifying the immune system. And, finally, the agency doesn't need me to defend it, but my understanding, Dr. Krueger, is that they have a program called Compassionate Clearance when, if a patient is very ill and needs a non-approved drug, certainly it can be used. And I've filled them out. They keep all kinds of data on it and you're allowed to treat your patient, but

that's not the way you try a new drug to see if it's going to be used on a population of people.

Thanks.

DR. McGUIRE: Bill, thank you.

Inevitably, there will be some redundancy between yesterday's program and today's program, since we're focused on a fairly narrow sector of biology.

We're really quite badly behind and I would like to hear from Dr. Duvic and then Dr. Siegel.

DR. DUVIC: I would just briefly like to counter what Dr. Rosenberg said. Even if psoriasis is a bacterial antigen-driven disease, there is still an abnormal immune response, and these agents represent a whole new class of agents that we need for our patients. None of the drugs that are currently available for psoriasis in the severe state are without side effects that are equally as scary as anything that these drugs could have as potential toxicities, including development of cancer, melanoma in the case of PUVA, immunosuppression, cirrhosis, renal disease or failure.

And so this is a really exciting opportunity in science to understand the immune response and to modulate it, and I think that industry and the FDA should be in very close partnership to see the development of these agents progressing in a very exponential fashion.

DR. McGUIRE: Okay, clearly stated.

Dr. Siegel?

DR. SIEGEL: Well, I have a question for Dr. Gottlieb, but I do want to respond briefly to Dr. Rosenberg's comments. I certainly concur that the immune system is very complex, and we've seen in any number of diseases that interventions often do not have the intended effect. But I would caution very much against simplifying it to the extent of brakes and accelerators, talking about up-regulation and down-regulation. The immune system has many arms and each of those arms has many functions in its own right, and virtually every intervention we do and virtually every disease we know has elements of hyperimmunity as well as elements of immunosuppression.

And I think the term "immunomodulation" actually allows more appropriate thinking than terms such as "immunosuppression," where the drug may, in fact, be in some cases immunosuppressive and in other cases immunostimulatory. So I just want to make sure we keep an open mind to the complexity.

My question to Dr. Gottlieb is for a clarification of a remark I thought you said that it would be unconscionable to ask patients to participate in placebo-controlled Phase 1 trials. Now, I concur with your remark that such trials are not required. Sometimes they're done,

and sometimes it's informative and sometimes it's not. It's not a major issue.

However, you left me and maybe others here with this statement and I don't understand the basis. I assume if you enroll a patient in a trial, you get informed consent. You explain to that patient. If the patient is not to be on treatment during the course of the trial, you tell them up front they're not to be on treatment during the course of the trial.

You also tell them as part of the informed consent process that at any time during the trial, if they wish to drop out of the trial and receive whatever treatment is most appropriate, they are totally free to do so. And then they either volunteer to be in the trial or not. So how or why would it be unconscionable to present that choice and decision to a patient?

DR. GOTTLIEB: First of all, the kinds of patients who are being asked to participate in these studies are like the ones that Jim Krueger showed. And most patients, even when they're faced with a placebo-controlled study--and I'll be honest with you; if I have a study that's not placebo-controlled, I'll recommend to the patient to go into this one. But if I have no choice and I have placebo-controlled studies, basically you can say all of these things and you can give them the ratios and everything, but most patients

in their heart say "I hope I don't get the placebo."

So I think that to have patients like the ones Jim showed--and despite what you say, they still are thinking "I'm going to get the active drug." Even if they sign into it, even if it's in bold-face, it doesn't make a difference. People still believe what they want to believe, and when the drug doesn't work, even though it's not appropriate, they say, "oh, gee, doc, I got the placebo." You know, it could be still the drug, but basically people in their heart think they're going to get the drug. And it is unethical to have that kind of person on no treatment for the better part of six months. That kind of person should be on chronic treatment.

And also taking your reasoning further, then if we had said in part of the protocol that part of this protocol will be that we will cut off your left arm, but that if you give informed consent and they understand it, it's okay, that kind of reasoning, I think, is a bit far-fetched.

DR. SIEGEL: Obviously, there are many other principles besides informed consent that go into ethics. I won't specifically address that. I would note, though, just for the record that placebo-controlled trials don't necessarily imply there's no treatment on the placebo arm. There are many placebo-controlled trials where the patients on the placebo arm are receiving many active treatments.

DR. GOTTLIEB: I don't think in the case of moderate to severe psoriasis you're going to get an adequate response on placebo.

DR. McGUIRE: With respect to both of the speakers, I think your positions are very well-known and have been well-known in our business for a long time. We need to move. We have a patient advocate, Dr. Jacqueline Goldberg, who's a new member of the Advisory Committee.

MS. GOLDBERG: I would just like to reiterate what Dr. Gottlieb said from the consumer perspective. I feel like in many situations, and especially what I've heard in the last couple days, in some of these placebo-controlled trials the buck is being passed to the IRB. And these kinds of things need to be decided--the ethics of this needs to be decided on a national level.

DR. McGUIRE: Dr. Mindel?

DR. MINDEL: I'd like to talk about it from the pharmacologic viewpoint and go back in history to penicillin and tetracycline. When patients were studied with a combination of penicllin and tetracycline, some died, and the reason was that penicillin was less effective in the presence of tetracycline because tetracycline stopped the cells from dividing and the penicillin only works on dividing cells, so that in combination therapy if tetracycline had been discovered first, penicillin would

have been shown to be an ineffective and dangerous drug and discarded. But, luckily, it was the other way around.

But sometimes combinations of drugs work less effectively, and you can discard a very effective drug like a penicillin. If tetracycline were given first, you would have discarded penicillin and said it was an ineffective or contraeffective drug. So there is a role for studies where combinations are used and there is a role for where individual agents are used. I have a feeling that that analogy between penicillin and tetracycline, dividing cells and non-dividing cells, is very applicable to the kinds of drugs that we're talking about now, these biological drugs.

DR. McGUIRE: Dr. Duvic?

DR. DUVIC: I think the point in this case is that if you're going to test biologics and require placebo-controlled studies and have a washout period where the physician knows the patient is going to get a lot worse and we're going to make a patient worse, not better, then you have to do these studies in less severe patients who can tolerate that. That's the whole point.

DR. SCHWIETERMAN: Let me just state for the record--

DR. SIEGEL: I wasn't even debating when or where they should be done, just that if they're done, they should be done with informed consent. And if they're done with

informed consent, it's hard to understand why we're throwing around words like it's unconscionable to ask the patient for informed consent if you do it appropriately.

DR. McGUIRE: Well, of course, these will be done with informed consent. Without trying to put any more spin on something--

DR. SCHWIETERMAN: I'd just like to clarify for the record we don't require placebo-controlled studies in Phase 1, nor do we require washout periods. We simply consider on a case-by-case whether those things are appropriate or not, given the agent, given the patient population, and given the risk and benefits involved.

DR. McGUIRE: And I think the investigators know that.

I would like to go on to Karen Weiss. Do you have some--

DR. WEISS: Given the time, and I don't really have anything to say, we already know what the focus of this morning's discussion is, so without further ado I'm going to introduce Dr. Krueger to kick off the open discussion.

DR. McGUIRE: Does Lou want to say anything?

DR. WEISS: Dr. Marzella will follow briefly with some general comments after Dr. Krueger's presentation.

DR. McGUIRE: For the transcriptionist, this is Dr. Gerald Krueger.

DR. G. KRUEGER: Thank you. One of the things that I didn't talk about yesterday--the reason the PASI was developed was to get around some of the problems of trying to do statistics on numbers between 1 and 4. They wanted a bigger range to work and by amplifying disease by the multipliers of legs versus arms versus trunk versus head and neck, they sort of shot themselves in the foot. And that was part of what I was trying to say yesterday and I should have said that by way of introduction.

What I'd like to do today is to talk to the Advisory Committee and to the rest of you about a story, and the story is psoriasis being mediated on an inflammatory and immune basis, and that story has, in my opinion, a considerable amount of evidence. What I'm going to do today is to go through with some speed I don't think I've ever accomplished before, but just to give you some highlights.

To start with, psoriasis is a disease that presents in unique parts of the body. It seems to have an inherited basis, and one of the questions that has to come to your mind when you think about an inherited disease is how can you have disease expression here and not here. And, likewise, how can you have a genetically-based disease that gets better and worse and can cause arthritis, can cause debilitating psoriasis such as you see here and we heard about in the last few days?

And the other part of psoriasis that I'd like to talk just a little bit about is what I all the biology of the disease. Before you have psoriasis, if you're a patient who does have the disease, you have what I call pre-psoriasis. You're genetically prone to have it. Then some trigger event occurs, clinical expression occurs. Once clinical expression occurs, it can move back and forth on a spectrum of disease.

When it moves over to the right, it tends to be in what we call a flaring state. At that point, if you injure the skin, it's likely that you can make psoriasis worse. And, likewise, when it moves to the other extreme, the disease tends to be more stable and when you injure the skin, you do not trigger further psoriasis.

It appears as though that inflammatory elements can move the disease back and forth, and the best illustration there are the flares that are associated with either generalized injury or infection. The fact that moves back and forth suggests that the body has regulatory factors that it can use to modulate the disease. And, of course, if there are endogenous regulatory factors, that means there's control of these regulatory factors. And given that everything that happens in life, except accidental death, is controlled by genes, that means that this is a genetically-regulated.

Let me now move on to what I call the underpinnings for an immune-mediated basis for psoriasis. When I grew up, as many in this room did, psoriasis was a disease of the epidermis with hyperproliferation. And then we did some experiments back in the early '80s that showed that involved and uninvolved skin developed epidermal hyperplasia when it was transplanted to nude mice. However, this transplanted skin did not display overt signs of psoriasis. Let me just share one data slide with you that illustrates this.

In this experiment, what we did was to transplant normal skin to immunodeficient mice, aphemic mice, and then follow an index of psoriasis which is epidermal proliferation, which is on this axis, over time. And when we did that, you'll note that there was basically no change in the normal skin. The involved skin started high and then drifted down to more normal levels, but still the epidermal proliferation was some two-fold higher than it was in normal skin. The surprising thing was that uninvolved skin became more psoriasiform with time.

What this experiment showed us was that involved and uninvolved skin in patients with psoriasis are equally prone to disease and that there is an inherent abnormality within skin. The curiosity was that despite this increase rate of epidermal proliferation, there was no evidence of

psoriasis in these mice, and that caused us to suggest at that time that more is needed than abnormal rates of proliferation to induce a lesion of psoriasis, namely you needed an active immune inflammatory system.

Other evidence that there is an immune-mediated basis for the disease has been suggested here already here in this meeting, bone marrow transplant. Curiously enough, if you need a bone marrow transplant and don't have psoriasis and have as your donor somebody who has psoriasis, the likelihood of you getting psoriasis increases rather substantively. Likewise, if you have psoriasis and get a bone marrow transplant from somebody who doesn't have the disease, it clears, and there are somewhere in the neighborhood of ten examples in the literature of this occurring.

Cyclosporine was, I think, an early bit of evidence that there is an immune-mediated basis of the disease. We know that because cyclosporine is very effective in the treatment of disease and it inhibits the generation of IL-2, which promotes T cell expansion and activation.

The other part of the story for the immune-mediated basis on the transplant side was conducted by experiments that were from the laboratory of Brian Nickoloff. And what he did was to transplant involved skin

to skin mice, not athymic mice, but the skin mice, and what he noted when he did that was that there was acanthosis and scale. There were many immunocytes that persisted. In our experiments, the immunocytes did not persist. In this model, they do persist and they have a cytokine profile that is HLA-DR-positive, ICAM-1-positive, and increased amounts of IL-8.

Transplantation of uninvolved skin to skids--many of the same things that we saw, namely the gaining of psoriasiform features, acanthosis, some human immunocytes, and the profile was HLA-DR-negative versus positive, ICAM-negative versus positive. However, there was an increased expression of IL-8. Normal skin did not have these changes.

More recently, his laboratory has injected autologous lymphocytes and these autologous lymphocytes will cause minimal acanthosis and angiogenesis in both uninvolved skin and normal skin. However, if they are activated with a superantigen plus IL-2, then you see many of the changes that Jim Krueger showed us yesterday of psoriasis.

And more recently, Brian has shown that the T cells that induce the psoriasiform change in this particular model are gamma interferon-producing CD4-positive, CD45RO memory T cells, and that the other part of the story is that injection of various stimuli into uninvolved psoriasis skin, condition media from activated peripheral blood mononuclear

cells, will lead to some thickness.

When you use the super from IL-2, superantigen-activated lymphocytes, not much occurs. KGF alone, not much occurs. However, if ykou take activated peripheral blood mononuclear cells and inject that into uninvolved skin on a mouse, you get a tremendous increase in thickness, suggesting that it's a cytokine mix that is made by lymphocytes that causes the epidermal proliferation seen in psoriasis.

The cytokine profile of involved psoriasis is a TH1 phenotype. This is work from the investigators listed here, largely from the Rockefeller, but also there's some evidence in support of that from our colleagues in Europe. T cells in involved psoriasis lesions are activated. They're CD8-positive in the epidermis, CD4-positive in the dermis. There's expression of IL-2 receptor. They secrete IL-2 with gamma interferon. And, importantly, as Jim Krueger noted yesterday, these decrease as psoriasis improves.

The T cells and antigen-presenting cells in the epidermis and dermis are proliferating. This is from Kevin Cooper's laboratory. And many of them display memory phenotype, which is very much in harmony with what I just told you in Brian Nickoloff's model systems. T cells isolated from the skin make cytokines that stimulate

keratinocyte stem cells from uninvolved skin, but not from normal skin, to proliferate, suggesting that there is an inherent aberration in skin of patients with psoriasis as well.

Move now from some of the experimentally-derived data to support the concept of an immune-mediated basis of the disease to response to therapy, and the first ones are pretty obvious. Jim Krueger and his colleagues have shown that conjugated diphtheria toxin to IL-2, given I.V., will cause in some patients a dramatic and rapid improvement, with moderate responses in others, not suggesting that these are therapies that we're going to be using. I'm just using this as evidence of an immune-mediated basis for this disease.

Anti-CD4: kill the CD4 cells and what happens? Again, relatively short courses of therapy. There's improvement. However, these patients, many of them, have prolonged suppression of their CD4 counts. When I was a boy, methotrexate worked because it damaged keratinocytes and I grew up with that. And then somebody comes along and says, well, you know, what does it do to lymphocytes? And the answer is it sends them to apoptic pathways and it does it a 1000-fold lower dosage than it inhibits keratinocyte proliferation. So a therapy that we thought was mediated directly on keratinocytes, in truth, has its largest effect

on proliferating lymphocytes.

How about ultraviolet light? Well, as Jim Krueger would tell you, and as he has written about, when you look at lesions of psoriasis, what you find is that the T cells are much more sensitize to induction of apoptosis than the keratinocytes.

PUVA. Again, the anti-proliferative effects of PUVA are similar in this experiement where peripheral blood lymphocytes and T lymphocytes were looked at, and they were more responsive to PUVA than human keratinocytes. The probable basis of the response produced by PUVA is likely via selective apoptosis of T cells in diseased skin.

How about topical therapies, corticosteroids, vitamin D3, vitamin A? Actually, they all too may have a common mechanism. The receptors for these belong to a supergene family and what you have is ligand binding, nuclear localization binding to specific sequences, and the induction or repression of target genes. And the possible mechanism that I think you could come to--and I only do this as a general--I'm trying to bring some basis for all therapies to an immune modulation--is to appreciate that NFAT complexes with AP1, which is a nuclear transcription factor, binds to IL-2 promoter and production of IL-2. It seems probable that putting the agents that I just mentioned on the previous slide on the skin, you have interference

with this complexing and IL-2 production.

If indeed there is an immune-mediated basis for a disease, it would make some sense that the T cell receptor should belong to a common--should have a commonality amongst patients with the disease, and indeed there is some evidence that this is the case. The T cell receptor is a polypeptide heterodimer that occurs on T cells, has an lot of ability to recognize many epitopes. And if a disease results from recognition of the same antigen by T cells, it is predicted that the molecular sequence of the T cell receptor should be the same.

Is that the case? The answer is in at least two different groups that T cells have been--when T cells are isolated from skin of patients with psoriasis and you look at the T cell repertoire, you will find the V beta 13.1 and the V beta 3 being predominant, and it's this that has led to some of the T cell vaccination trials that are going on.

Let me just quickly give you where we are today, actually, in understanding the genetics of this disease. I put this together on 10/1/98, and when you're putting together slides on understanding the genetics, you probably should put the hour down as well. But on 10/1/98, here are some of the things that we know.

First of all, we're quite sure that psoriasis is genetically acquired. The reason for that is there is--in

afflicated members, 30 percent of them will have a family history of disease. If you look at identical twins, the likelihood of concordance for disease is around 70 percent. And the question that has gone on for a long, long time and is going to continue to go on is one gene, two genes, and has the psoriasis gene been found.

There's been a large genome scan in several kindreds and at this point they have found two loci that are associated with psoriasis. There's one on 17Q and one on 4Q. And there has been a genome search on affected sib pairs and a major psoriasis susceptibility locus has been localized to 6p21 of the major histocompatibility complex, and that currently is running with a p of less than 6 times 10 to the minus 8. The likelihood of being wrong on this one is pretty low, and so this one is being referred to as the psor1 gene. Currently, this locus has been narrowed to 250 kilobases of the major histocompatibility locus and it is likely this locus that's the reason for the well-known linkage to CW6.

Unfortunately, the genome-wide search has also found evidence that there is some evidence of susceptibility at 1, 2, 4--I've already talked about 6--8, 10, 11, 14, 16. Sixteen is very interesting because the linkage there is very close to that of Crohn's. Crohn's disease has represented some two to four, or maybe even a higher-fold

expression in patients with psoriasis. Seventeen, we already talked about, and 20. Psoriasis is likely a multigenic disease. The National Psoriasis Foundation is currently sponsoring an analysis of 850 afflicted sib pairs using common marker panel to determine which ones of these are true susceptibility loci.

So the last two slides, conclusions. Uninvolved and involved skin, the patients with psoriasis have inherent defects. That's characterized best by increased epidermal proliferation and probably an enhanced response to inflammatory mediators of activated T cells. Further, activated T cells are necessary for expression. Without activated T cells, you do not see the disease, and the reason that we say with emphasis is the experiment where injection of T cells into uninvolved psoriasis skin that were activated led to psoriasis. Injection of T cell cytokines leads to psoriasis. Anti-CD4 leads to clearing. Treatment directed against IL-2 leads to clearing. What is the molecular basis of the autoimmune nature of this disease? That's to be determined. What is the antigen? That's to be determined. How is the psor1 gene involved? We don't know.

Thank you. That was short.

DR. McGUIRE: I was going to say that. Thanks for doing a big job in a short period of time. The Advisory

Committee has some questions to consider and before we do that, Jerry, we could discuss your discussion all day and so we're not going to do that.

DR. G. KRUEGER: I'm hurt.

DR. McGUIRE: Well, I'll pay later.

DR. G. KRUEGER: Okay.

DR. McGUIRE: Lou, did you want to say a few words about complications?

DR. MARZELLA: Just a very few brief comments to reinstate basically the fact that a number of serious adverse events have been observed in clinical trials of immunomodulatory agents to date. These essentially fall under the following categories: cytokine release syndrome, and the mechanisms of this syndrome are being evaluated. The clinical manifestations are similar to those that have reported for other products, for products which are in the open literature.

The other syndrome is vascular leak syndrome. Again, the mechanism is poorly understood. However, the clinical manifestations and significance is similar to that that has been observed and reported for other products. Finally, immediate hypersensitivity has also been seen, and again the clinical features here are typical to what every clinician recognizes. A number of Phase 1/2 study designs are being used and are currently being discussed.

And so in summary, then, it would seem from the safety data to date that a continued cautious approach to development of biologics is warranted, and that as is obvious from the discussion here, questions about optimal clinical trial design remain, and optimal patient population to study. And we'll look forward to the discussion of that in the open session.

DR. McGUIRE: Thanks, Dr. Marzella.

If the Committee will go to the bottom of page 10, these are questions that DODAC has given us. Composition of patients for early clinical studies: New biological therapies for psoriasis have typically been evaluated first in patients with stable, moderate (often defined as disease involving at least 10 percent of total body surface area) to severe plaque psoriasis of at least 12 months' duration. Patients with mild plaque psoriasis are often excluded from early clinical studies of biological therapies, as are patients with guttate, pustular or erythrodermic psoriasis.

Generally, patients in early studies have a history of previous systemic treatments; have failed, or are ineligible for treatment with chemotherapy or phototherapy, including PUVA, UBV with tar, methotrexate, cyclosporine, and oral reinoids; have an absence of active or chronic infections or neoplasia; and have evidence of adequate bone marrow and immune function. Washout of systemic and topical

antipsoriatic therapy is performed in many studies.

Some sponsors have proposed other entry criteria for early studies. These criteria include skin involvement consisting of 5-percent TBSA with or without involvement of certain critical body parts or areas, documented history of failure of topical therapy, or evidence of marked effects of disease on quality of life.

Question one: Given the clinical safety profile of some biological agents and the potential risks associated with their use, should studies of these agents be reserved for patients with moderate to severe disease? Let's have discussion on that first piece before we go to the second part.

Dr. DiGiovanna?

DR. DiGIOVANNA: I don't like the word "studies." It's too broad. I think we want to focus here, are you talking about early studies, late studies? Certainly, Phase 4 studies wouldn't be--

DR. McGUIRE: Let's say Phase 1.

DR. WEISS: Yes. The heading of this section was called "Patient Population for Early Clinical Studies," so we are talking about the early Phase 1, early Phase 2 perhaps.

DR. McGUIRE: Okay, so we're talking about Phase 1. How restrictive do you want to be for Phase 1?

DR. DiGIOVANNA: Well, I think this includes patients with moderate involvement, the way it's worded, and from my reading of it that's the sense I got that what people were looking for, patients with moderate involvement for early studies, and not patients with mild involvement. So I would think that this is an appropriate statement.

DR. McGUIRE: At least 10 percent or as little as 5 percent?

DR. DiGIOVANNA: The question didn't ask me that.

DR. McGUIRE: What?

DR. DiGIOVANNA: It didn't ask that. That's a--

DR. McGUIRE: Well, but that's stated in the first paragraph, and then the question is do you want to be less rigorous and treat subjects with skin involvement consisting of 5 percent with or without involvement of certain critical body parts.

Dr. Duvic?

DR. DUVIC: I feel like a broken record, but these drugs do have potential toxicity and I think it's less likely that you would get the toxicity of some of these forms of toxicity in less advanced patients, especially capillary leak syndrome. In psoriasis, you have a lot of angiogenesis with a lot of T cells around the blood vessels, and if you've got 90 percent of your body covered with psoriasis, then you've got angiogenesis over the same

amount.

And I believe that the capillary leak syndrome may result from lyses of T cells around blood vessels that results in damage to the vessels and capillary leak. So I think you're going to see more severe capillary leak in more advanced patients. I think the immediate hypersensitivity reactions are kind of idiosyncratic. They're going to happen in everyone, and the cytokine profiles are probably going to happen in everyone.

It's important to have some severe patients in your Phase 1 studies so that you don't miss toxicities that would occur in these patients, but I think it's in the interest of drug development for this group of patients to open it up a bit and to have some minimum disease that you have to have. I mean, maybe it's 5, maybe it's 10. I don't know. I would be happy with 5 percent or patients that can't tolerate or are failing the therapies available to them, but to open it up a bit and not require that it be done in the most severe patients.

DR. McGUIRE: We looked at the NPF document yesterday, the categories that they identified.

DR. DUVIC: Right.

DR. McGUIRE: And moderate, by their definition is--

DR. DUVIC: Is 2 to 10 percent.

DR. McGUIRE: --2 to 10 percent.

DR. DUVIC: And also body part area could be considered as more severe based on the quality of life or change in function of the patient.

DR. McGUIRE: And there are exceptions for disease on palms, face, feet, genitals, other areas that compromise quality of life.

John, did you want to respond again?

DR. DiGIOVANNA: Yes, I did. It's rare that I disagree with Madeleine, but I think while everything you say is true, the way you say it clouds the issue. I would agree that patients with 90-percent body surface involvement may have other issues related to the activity of the disease, but that's not the question here. The question here, as you and as our fearless leader are defining it, is 2-percent body surface area is sufficient involvement for initial exposure to a drug which is potentially life-threatening, and I think that's the other pole.

DR. DUVIC: I don't feel that 2 percent is enough. My own opinion is that you should have 5 to 10 or extenuating circumstances, but that you shouldn't require patients in the most severe category of psoriasis, the unstable patients that require systemic therapy, to be the only subjects in which these drugs are tested.

DR. McGUIRE: Well, I heard the other side of what

Dr. Duvic said, which is that she does not want to expose erythrodermic or patients with very extensive disease because of the possibility of complications. I don't think it would be very productive to talk about the difference between 2-percent and 5-percent involvement. Unless you really, really want to, I don't want to.

DR. DiGIOVANNA: Well, I'm saying the definition of moderate you're talking about, it goes down to 2 percent.

DR. McGUIRE: Right.

DR. DiGIOVANNA: I'm not even so sure that 5 percent is sufficient for initial exposure to a drug. I mean, we're probably not talking hundreds of individuals. We're probably talking, I would think, dozens of individuals.

DR. McGUIRE: Dr. Gerald Krueger?

DR. G. KRUEGER: You know, again, you know, psoriasis as severity, body surface is only one parameter, and don't get focused on it just because that's so easy to see. And number two is that, you know, I don't see much difference between someone with 2-percent psoriasis, who it bothers them, who reads informed consent and agrees to have, as John says, a potentially life-threatening drug--I don't see much difference from that person than from a normal human volunteer who reads that same informed consent and agrees to do it. I'm sorry. I'm apparently on the opposite

side here. We went over this yesterday, but it's worth saying again, I think, today, maybe several times.

DR. DiGIOVANNA: I think we're on the same side. I agree.

DR. McGUIRE: Okay, fine. I omitted part number two which I should have included. I thought we could discuss that separately, but it really has a major influence on part one, which is please discuss the criteria mentioned above for assessing severity of disease. Are there other additional inclusion or exclusion criteria or modification of the above criteria that sponsors should consider for studies of patients with psoriasis?

Dr. Duvic has said she's concerned about the generalized erythrodermic patient, and I don't have experience with these biological modifiers to agree or disagree.

DR. DUVIC: I think the point that the clinician makes in taking care of these psoriasis patients is when do you need to go to a systemic therapy? When can you no longer control the patient with a topical agent? And that's really the cutoff, and if it's a person with palm or Plantar psoriasis, they may only have 2 percent of their body surface involvement. One palm is 1 percent. But yet they may not be able to walk or work and need methotrexate, need a systemic therapy. That's really the cutoff and it varies

from patient to patient. I think that's what Jerry said.

DR. McGUIRE: I would like to have heard also that it depends upon the site of involvement and whether the patient has failed other therapy, or other therapies have failed the patient. And so you would be dealing with patients who had pretty much run the course of various therapies. These would not be entry patients, I would think.

Jerry, are we close in terms of entrance criteria?

DR. G. KRUEGER: You know, every once in a while I think we are and then I hear you say things that end a sentence just like you did and I'm not sure.

DR. McGUIRE: What didn't ring true?

DR. G. KRUEGER: As you said, you weren't sure about whether or not those patients should be entered.

DR. McGUIRE: No, no, patients who had--one of the entry criteria would be having conventional therapy failure, and so this would put them into a higher priority range. That's what I should have said.

Dr. Rosenberg?

DR. ROSENBERG: I think, you know, we may be in danger of blurring what we're trying to do. The first studies are to assess safety. We don't need to mix that in with what will be the claimed indication, which comes much later after we know an awful lot about safety and an awful

lot about efficacy and I mean well down the road. And I don't think we need to confuse these two separate issues.

DR. McGUIRE: I don't think they're confused. We're talking about patients in whom the potential benefit is somehow commensurate with the risk because we're dealing with agents, with biological modifiers that have very limited play.

DR. ROSENBERG: Well, by benefit, that's not so because the patient who gets into a Phase 1/Phase 2 trial is not going to be benefitted by this drug until it clears and comes out for sale. They're not going to stay on it. It's not a way to treat you. This is a way to learn. Isn't that right? They don't stay on this drug, do they?

DR. SCHWIETERMAN: Well, actually, we have a number of studies where after the initial, if you will, rigorous testing period, there are open-label extensions whereby patients can continue on. Whether they're done in Phase 1 and Phase 2, it depends on the product. It depends on a lot of things, but it's not right to say that once they have completed the Phase 1 study, they have to wait for the marketed product before they can benefit in all cases.

DR. McGUIRE: Dr. Miller, do you have comments?

DR. MILLER: No. I would reiterate what Madeleine said that, you know, restricting to certain percentages of body involvement really could preclude people who need it.

And extenuating circumstances have to be looked at, and quality of life.

DR. McGUIRE: Is that informative enough for the agency? It looks like it's not, okay.

DR. WEISS: I want to clarify something that Dr. Duvic said, talking about the time where somebody reqauires systemic therapy. What do you mean? That's the point in time when they should be considered for these trials to the point where after they've tried the systemic therapy and have failed or are not doing as well? I'm a little confused about what that critical juncture is.

DR. DUVIC: I was trying to clarify in your mind what the clinician and the patient feel is more moderate to severe disease. That's when systemic therapy is necessary. I don't have a problem doing Phase 1 trials in normal human volunteers if they're informed, okay, for safety, and I think that the mild, topically-treated psoriasis patients fall into that category. They're normal human volunteers.

I think that ultimately these drugs will be used to control the more severe patients, but I don't think that the Phase 1 safety trials have to be confined to this most severe group of patients. Certainly, they have to be included in the database, but I think they're more likely to have toxicity or cumulative toxicity.

DR. WEISS: Okay, thank you. That's clear for me

now.

DR. SIEGEL: Dr. McGuire, in suggesting that the patient should have failed prior therapy, were you specifically talking about topical therapies or suggesting that they also have failed aggressive systemic therapies?

DR. McGUIRE: I don't know, but I suspect that many of the subjects who are willing to participate in this kind of clinical trial will be those who have had bad experience with their psoriasis and who have not had the kind of response that they wanted. Now, that's different than what--that's a different category of information than you've heard from Dr. Duvic, who is willing to treat a normal volunteer. But I think the volunteers are probably going to be people who have had problematic psoriasis. But this is just me talking; this is not the Committee talking.

John, do you have any other comments?

DR. DiGIOVANNA: I'm just a little confused. I think that to one extent I'm trying to frame in my own mind what the purpose of answering the questions are. And if the agency is willing to do Phase 1 studies in normal volunteers, then there really is no reason to restrict entry criteria to moderate involvement, nor to define it in any particular way because certainly any of those patients would be as appropriate as normal volunteers.

And certainly, as Dr. Duvic suggested, those

individuals who had some severe disease, including erythrodermic psoriasis, would not be the optimal candidates. And I certainly agree with Dr. Krueger that someone who has 2-percent psoriasis is the same as a normal individual. So I think from that perspective, there was really no reason for the question.

But if one is looking, for whatever reason, to identify someone to establish a risk/benefit ratio of some sort, whetehr the FDA is interested in that, the company is interested in that, or the IRB is interested in that, then someone might want to create criteria to say when is an individual affected substantially enough that they, as Madeleine suggested, would require systemic therapy and have that sort of psoriasis that's weighty enough to be of value in that benefit.

DR. McGUIRE: That's the way I interpreted the question because certainly all of those groups will be in on this decision and the IRB will be a limiting factor.

DR. SCHWIETERMAN: Let me just make one brief comment. I think part of the confusion arises that we're talking about general principles and abstract thought when the particulars of risk/benefit, when you're faced with them, become quite a bit more obviously real and complicated, so that the appropriateness, per se, of normal volunteer studies very much depends upon what you're talking

about and the types of toxicities you want to see. But I think that what we were after with this particular question was the Committee's sense, and this has been very helpful for us, about the kinds of things that should be considered when we assess the risk/benefit.

DR. MARZELLA: If I may, another comment to what Dr. Duvic was saying that we are looking for that information. For instance, one of the possibilities is that there might be an adverse reaction in psoriatic patients which may not be seen in normal patients. And, you know, the typical example that you suggested that there may be a population of T cells which is activated around vascular areas and may, you know, induce vascular leak when you dose--it's something that we would like to learn, if possible, during early trials.

And while it may not be appropriate to obviously look for that toxicity in patients with very severe disease, we're looking for something intermediate where there will be some manifestation of disease. And if there's drug-disease interactions, they will become obvious before we go into large-scale, blinded studies.

DR. McGUIRE: Okay. Let's go to design of safety studies. Early studies generally are uncontrolled, open-label studies that use single-dose regimens. Frequently, the starting dose level is chosen to have an anticipated no-

effect based on the available pre-clinical pharmacokinetic and pharmcodynamic data. Certain sponsors have asked CBER to consider other safety data designs for immunomodulatory agents that include intra-patient dose escalation, starting dosing levels that are likely to be bioactive, enrollment of patients with mild disease in single-dose studies in which no clinically meaningful pharmacologic activity is expected, allowing concomitant stable drug treatment to continue, et cetera. Please comment on appropriate study designs for biological therapies for psoriasis.

Four: The incidence of certain serious adverse events (e.g. neoplasia) is likely to be low and the time of onset of clinical manifestations delayed following treatment with certain biologic products. Please discuss the duration of follow-up necessary to assess the safety of these products. In addition, please discuss mechanisms (e.g. registries) that might enable capture of data on long-term adverse events such as opportunistic infections, neoplasia, and autoimmune disease.

We actually talked about item 4 pretty extensively yesterday in terms of post-marketing surveillance, which is complex, expensive, informative and open-ended. And I mean we can talk about it some more today, if you wish, but let's concentrate first on the issues in the lead paragraph--intra-patient dose escalations, starting dose levels that

are likely to be bioactive versus levels that you're pretty sure are not going to work.

John?

DR. DiGIOVANNA: I think that all of these and probably, as time goes on, many other ways of designing, and strategies for designing, clinical studies should be available. And if there's a guidance to be written, I think it should incorporate that, not only what we can think about now, but also what will be developed, I think, as time goes on and based upon the practicalities of conducting these studies.

I think that by being creative you can get lots of information, and you can also solve some of the issues, I think, that have been raised without much extraordinary change in the status quo. So if you're very interested, for example, in looking at a particular agent for a one-time exposure and the patients that are involved may derive very little benefit from that, then that one-time exposure can be attached to a subsequent phase of the study where the patients will receive a drug for multiple doses.

And then one could evaluate the effect of that drug on a novice patient who's never seen it and a patient who has already had it, and possibly at both an intra- and inter-patient cohort approach where the individual patients are being escalated so that they do--if they do start at an

inactive dose, they will have a dose that's likely to be active at some point, versus starting different cohorts at different escalated doses so that you can see how the novice patient at a higher dose reacts.

In addition, there's no particular reason in my mind why--while, granted, the idea is to expose the fewest individuals, why that cannot also be stratified so that for those patients who are able to come off of therapy possibly with a washout period, that may be one component of a study, whereas patients who may be able to be maintained on possibly not the most strongly active medications, but possibly a variety of topicals or other agents, or even light treatments under some schedule could be offered, the combination of having an active drug while on some kind--I'm sorry--having the potentially active drug and maybe even a placebo, with the understanding that there is also therapy that's going to be maintained at a certain level which is possibly something that's been done with other sorts of disease related psoriasis. So I think this should be more expansive rather than exclusive.

DR. McGUIRE: Well, we're talking about Phase 2/Phase 3 studies here. But you're talking about early, open-label studies and it is quite possible that you will learn something early in the Phase 2 studies that will help design the study. And I agree with what Dr. DiGiovanna is

saying that you would like to have the flexibility at that point to design it around your early observations.

DR. SCHWIETERMAN: Yes. In large measure, the phase becomes semantics.

DR. McGUIRE: Right.

DR. SCHWIETERMAN: That's called the second part of a Phase 1 study or Phase 2 study, but I agree with your positions and thank you.

DR. McGUIRE: Dr. Kilpatrick?

DR. KILPATRICK: Is it appropriate to talk about Phase 3 studies in this context?

DR. McGUIRE: Sure.

DR. KILPATRICK: Okay. I want to continue what John has been talking about, but I want to address Phase 3 studies for psoriasis. The FDA traditionally uses the randomized clinical trial for Phase 3 studies, and I accept that these are the gold standard in clinical research. However, for evaluation of biologic therapies for psoriasis in Phase 3 trials, after all we've heard today and yesterday, I'm wondering whether there isn't going to be a role for what I call sequential clinical trials.

And forgive me if I go on a little bit if you know all about these. These are typically still two-arm, randomized clinical trials, but they are not fixed sample size. Indeed, rather, pairs of subjects are recruited and

randomized one to each arm and followed until an outcome. Other pairs are recruited and entered in the same fashion either sequentially as they occur or after the first pair has come to an effect, has been plotted.

This design allows for early stopping, obviously, because you have a protected alpha level. This allows for early stopping in the case of adverse effects or if a significant difference between two therapies or a placebo and a therapy is detected at a given point. It's a cumulative plotting thing.

There are some difficulties from this design. It may take longer to accomplish, but theoretically--and it may--well, I'll go on to that. It should optimally reach a result with a minimum number of patients exposed to perhaps ineffective treatment. There are various types of sequential clinical trials, open and closed. Closed ones prevent the trial going on forever if the two treatment arms are, in fact, the same.

DR. McGUIRE: Eva, because of the way the table is configured, I haven't really asked you very many questions this morning. Would you like to comment at this point?

DR. SIMMONS-O'BRIEN: No. I would just say with the previous points that we have made already that I agree in terms of really taking it on an individual basis in terms of the patient selection, but I don't have any comments on

that.

DR. McGUIRE: I spoke from memory on item 4 in terms of monitoring potentially serious adverse events and I wonder if any of the members of the Committee would like to comment on that.

Dr. Rosenberg?

DR. ROSENBERG: I think, again, and hope to put more precision into this, these are powerful drugs which are used because there are people who need help. We've all heard that, and I think we need to keep it clear. Do we want something as a first aid, ultra-short treatment that would help people over a really tough, terrible flare, get in and get out, without the even higher rebound that we fear from cortisone?

I mean, cortisone is certainly the most effective thing to clear a flare, but then often you're worse off afterwards. And it's hardly ever used, but every once in a while it is. So there's a place for something that's almost as good as cortisone that doesn't have that follow-up rebound. I mean, something like that--the follow-up, I should think, would be three months to six months after they've taken it for a week, but the indication ought to be for a week and not that this is a drug that's, quote, "good for psoriasis" and we're worry about the long-term toxicity later.

We heard--I mean, at least I talked yesterday about cyclosporine two and four years on. You know, if it's going to have a place, apparently, it's going to be as a short-term drug. Then this is a chronic disease. If any of these drugs are going to be safe enough and seem appropriate for patients to take them on sort of an open-ended basis, then I think the studies ought to be constructed that way. And as a minimum, I think everybody who gets one of these drugs should be kept in touch with from the day he or she takes it until the day that FDA votes to approve or not approve that agent to see not only toxic effects or malignancies or superinfections, but also whether the disease becomes harder or easier to care for than pre-drug.

DR. McGUIRE: So you would endorse the concept of a registry?

DR. ROSENBERG: Absolutely, which ought to be maintained certainly until the day that it goes from three to four and they start selling it, and that's, I think, not too hard to ask of a sponsor.

DR. McGUIRE: Dr. DiGiovanna?

DR. DiGIOVANNA: I have two questions and I need an answer to the first one before I go to the second one, and that is it's my understanding that there are some drugs of this class that are approved for other indications.

DR. WEISS: There are a number of biologicals that

are approved. We recently approved two monoclonals for the setting of renalallograft prophylaxis in combination with other immunosuppressive therapies. OKT-3, which is a prototype, was approved about ten years ago for treatment of rejection episodes in renal transplantation. That's the one where we have probably the most experience about cytokine release syndrome.

As you heard or may know, we have discussions and open discussions at advisory committees. The anti-TNF receptor, Embrel, was discussed just last month for rheumatoid arthritis and recommended for approval. The DAB IL-2 fusion protein was presented and dicussed at open session of the Oncology Drugs Advisory Committee in early June and recommended for approval.

DR. SCHWIETERMAN: Infleximad [ph].

DR. WEISS: Infleximad, that's right; I happened to forget. We have an agent, a monoclonal antibody, to TNF that was discussed at the GI Advisory Committee at the end of May for use in Crohn's disease. That one is interesting when Dr. Rosenberg is talking about uses of single dose to treat an acute event and then issues about longer-term use. It's a situation actually we discussed extensively at the GI Advisory Committee with Infleximad, the monclonal to TNF, because those studies were done using the agent as a single dose; in a chronic Crohn's disease, a chronic disease,

showed remarkably good effects as a single dose that lasted for a number of months, on the average. And the Committee was very impressed to the point where they recommended approval. And post-marketing studies are going to be looking at evaluation of the agent long-term continuously, long-term intermittently, et cetera.

DR. DiGIOVANNA: So the agency has a lot of experience with diseases somewhat unlike like psoriasis where the renal transplant population would have lots of other immunosuppressive agents on board and with diseases not so unlike psoriasis, like rheumatoid arthritis. So my question is then how do you monitor for these long-term potential events in those other diseases where it may be similar or even more likely to see those, and can you use that to model how you'd do it for psoriasis in an appropriate way?

DR. McGUIRE: That was your real question.

DR. DiGIOVANNA: That was the real question.

DR. McGUIRE: That was the question that we were getting ready to take.

DR. SIEGEL: And the answer is that it's very difficult to do. And, in fact, I think the experience with drugs is similar. If you look at chemotherapeutic agnets that have the potential to cause malignancy or immunosuppression leading to infection, the amount of good,

hard, controlled data about how much they do that is limited and usually, to the extent it exists, emerges epidemiologically many years after approval.

Having said that, we do, in fact, collect, as Dr. Rosenberg suggested, typically data from the time enrolled on study to the time of approval. Often, there's a control in those Phase 1 and 2 studies, but as has been implied in some of the discussion there, what we frequently see is a control arm and a serious disease often doesn't stay on placebo. But at some point, because of ethical reasons and patient management, either it's put on other active therapies or is allowed to switch over to the controlled drug.

So when you see incidences of a few cases here or there of serious infections or of malignancies, it's often difficult to tell what to make of that. You can compare it against epidemiological data with experiences, you know, limited to a few hundred patients or 1,000 or a little over 1,000 patients, such as we've seen in some diseases. It's very hard to draw conclusions and we ask companies to commit to collect data in the post-marketing period. In most of the drugs we're talking about, to the extent those that are approved, time is short. So it's hard to know what that will reveal, but I suspect it will be like drugs. Over time, you'll get a bit of a feel from an epidemiological

study as to whether those drugs increase the incidence of certain types of tumors or infections, or not, but it's not a simple test.

DR. DUVIC: I think the dermatologists have been successful in long-term follow-up in PUVA from the patients who were treated in the '70s. So there is a good role model for this kind of follow-up, and I think that that kind of long-term follow-up is really useful for patients and their physicians in managing risk/benefit.

However, in your severe patients, they've seen a number of other immunosuppressive agents already and you're not going to be able to tell in that group of patients what the toxicity is actually due to. Is it because they took cyclosporine five out of ten years or is it because they got one of these agents? So, that makes the case for using some untreated patients in your database.

DR. WEISS: May I ask a question for the experts? Are there epidemiological studies in psoriasis? Well, I guess there is. You mentioned with PUVA and the skin cancers. Are there epidemiologic data coming up now that methotrexate and cyclosporine are being used with respect to evaluating for like lympho-proliferative disorders?

The same questions came up when we discussed Crohn's disease and we discussed rheumatoid arthritis, and what were presented to us at advisory committees were these

large epidemiological databases which are, you know, maybe the best you can get. But I was just curious to know, is there a background rate in these patient populations with this background of immunosuppressants?

DR. ROSENBERG: Those two papers from Toronto discussed that. By and large, they were, I think, the first, and it was specifically psoriatic arthritis. And when I read those, I went trying to see what I could on psoriasis, just the question you asked. In a not very exhaustive or skillful, perhaps, search for those references, I didn't find any that I thought were helpful.

DR. McGUIRE: Madeleine, go ahead, and then Dr. Gottlieb.

DR. DUVIC: There is a database on methotrexate-induced liver disease in psoriasis patients. I'm not aware that any of the agents used so far have demonstrated an increased risk of lympho-proliferative diseases in the literature.

DR. McGUIRE: Dr. Gottlieb?

DR. GOTTLIEB: I think that you have good resources here, the Novartis folks who are here, because I've heard publicly presented they are running databases and keeping track of lympho-proliferative disorders as a result of cyclosporine. And I think you probably should address one of the folks with Novattis here for the details of that.

So, that does exist.

And, second of all, I'd like to correct Dr. Rosenberg in the sense that Dr. Zacharias' recent paper is not the first paper on long-term effects of cyclosporine on renal function. Again, Rachel Grossman is sitting in the audience and she had a paper. I mean, there have been a number of studies that have shown long-term renal effects, maybe not with biopsies, but this is not of recent duration. That particular drug is monitored for long-term effects for years and I think the FDA is well aware of that.

DR. McGUIRE: If anyone from Novartis would like to comment on that issue, this would be the time to do it.

DR. ABRAMS: Hello. I'm Dr. Abrams from Novartis. We have a few Phase 4 commitments that we have begun to do mostly dealing with rheumatoid arthritis. The FDA has asked us to look at what has happened to patients that were in earlier clinical trials who were given high doses of cyclosporine who were allowed to continue with increased keratinines. And they would like us to follow them for up to five years to see what happened to those patients and that study is about to begin in the next couple of weeks.

There's also ongoing development of a registry for the rheumatoid arthritis patients that would be looking at these patients both in combination with other therapies as well as cyclosporine by itself, and that will be followed

for up to five years. In the psoriasis population, actually, we don't have any registries planned at the moment.

DR. McGUIRE: Okay. Those models will be very helpful for other long-term studies. Thank you.

Dr. Miller?

DR. MILLER: I would just say I think the issue of registries is crucial and that registries should, in fact, be set up for all of these preparations. And, you know, maybe the pharmaceutical houses are the ones to help us with that, but I think it's important that we know several years down the road what is happening because there are other instances where, you know, what was done years ago, we're seeing the side effects and the results, the ill effects of those therapies. I think if we get these medications approved, we should certainly follow and see what happens.

DR. McGUIRE: I think the Committee would agree with that position.

Dr. Wilkin, you've stayed out of the CBER business this morning. Do you want to get in it?

[Laughter.]

DR. WILKIN: No, thank you.

DR. McGUIRE: Okay.

[Laughter.]

DR. McGUIRE: Would the agency like to ask us to

address any questions that we've overlooked or I have read through or missed?

DR. SCHWIETERMAN: I don't think so. I think this has been very helpful.

DR. McGUIRE: Okay.

DR. SIEGEL: Were there not enough questions?

[Laughter.]

DR. McGUIRE: Committee, you have the last opportunity to say something on this issue.

[No response.]

DR. McGUIRE: We're adjourned until 1:00. Thank you.

[Whereupon, at 11:47 a.m., a luncheon recess was taken.]

AFTERNOON SESSION

[1:11 p.m.]

DR. McGUIRE: This afternoon, we're going to talk about tinea capitis clinical trials. This is an issue that has been under consideration for some time and I'm quite eager to get into the discussion. This is the 50th meeting of the Dermatologic and Ophthalmic Drug Advisory Committee, and we will start with Dr. Wilkin and introduce the people around the table.

DR. WILKIN: Jonathan Wilkin, Director of the Division of Dermatologic and Dental Drug Products.

DR. McNEIL: I'm Mike McNeil and I'm from the Centers for Disease Control in Atlanta. I'm a medical epidemiologist in the Mycotic Diseases Branch.

DR. FALLON-FRIEDLANDER: Sheila Friedlander from UCSD and Children's Hospital in San Diego. I'm a pediatric dermatologist.

DR. BABEL: Dennis Babel, clinical mycologist, Midwest Cutaneous Research, in Michigan.

DR. FRIEDEN: Ilona Frieden, pediatric dermatologist from the University of California in San Francisco.

DR. SIMMONS-O'BRIEN: Eva Simmons-O'Brien, Departments of Dermatology and Internal Medicine, Johns Hopkins, Baltimore, Maryland.

DR. KILPATRICK: Jim Kilpatrick, biostatistician with some exposure to epidemiological methods, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia.

MS. RILEY: I'm Tracy Riley. I'm the Executive Secretary to this Committee.

DR. McGUIRE: I'm Joe McGuire, Pediatrics and Dermatology, Stanford.

MS. GOLDBERG: Jackie Goldberg, consumer rep.

DR. TSCHEN: Eduardo Tschen, Department of Dermatology, University of New Mexico.

DR. ELEWSKI: Boni Elewski from Cleveland, Ohio, Case Western Reserve University.

DR. MINDEL: Joel Mindel from the Departments of Ophthalmology and Pharmacology, Mt. Sinai Medical Center, New York.

DR. DUVIC: Madeleine Duvic, Dermatology and Medicine, MD Anderson Cancer Center, Houston, Texas.

DR. MILLER: Fred Miller, Department of Dermatology, Geisinger Medical Center, Danville, Pennsylvania.

DR. ROSENBERG: Bill Rosenberg, Dermatology and Preventive Medicine, University of Tennessee College of Medicine, Memphis.

DR. DiGIOVANNA: John DiGiovanna, Department of

Dermatology, Brown University School of Medicine, and Adjunct Investigator, National Institutes of Health.

DR. McGUIRE: I'm beginning to get the picture. This is the constant region and this is the variable region, and it has taken me a day-and-a-half to figure that one out.

We will have the necessary conflict of interest statement read by Tracy Riley, Executive Secretary.

MS. RILEY: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the Committee participants, it has been determined that all interests and firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions.

Since the issues to be discussed by the Committee at this meeting will not have a unique impact on any particular firm or product, but rather may have widespread implications with respect to an entire class of products, in accordance with 18 U.S. Code 208(b), each participant has been granted a waiver which permits them to participate in today's discussions. A copy of these waiver statements may

be obtained by submitting a written request to the agency's Freedom of Information office, Room 12A-30 of the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record. With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. McGUIRE: Thanks very much.

Let me introduce Dr. Jonathan Wilkin again, who will make introductory remarks for this session.

DR. WILKIN: Thank you, Dr. McGuire. Over the last several years, I've been reading in the non-peer-reviewed literature--you know, those journals that show up that you don't pay for that cross your desk, euphemistically I think called throwaways, but I don't throw everything away. I save articles out of them and here's one that says "Update Shows Pediatric Tinea Capitis Is on the Rise." Another one: "Pediatric dermatoses: Time for a Change in Tinea Capitis Treatment." Another article: "Pediatric Dermatologists See New Treatments for Infectious Diseases:

Children Have Increasingly Better Options for Beating Tinea Capitis." Another: "New Ammunition Available to Fight Tinea Capitis."

And then, of course, in the peer-reviewed literature there are also papers out on some of the newer antifungal drugs and their use in the treatment of tinea capitis. So I thought that this was an emerging public health issue and that it would be a topic that would be very reasonable for the Committee to give advice to the agency on the rather complex issues related to the clinical trial designs in tinea capitis, much more complex than studying the other dermatophytes. So, that's the essence of that meeting.

In that spirit, we invited a group of folks that we believe to be very expert in this area and so at the beginning of the afternoon, after the open public hearing, would essentially be a CME type of session where we would all be brought up to date by these experts on tinea capitis and then go into some questions on clinical trial design issues.

DR. McGUIRE: Thanks, Dr. Wilkin.

The open public hearing will occur now. I only have one name and if anyone was planning to speak, let Ms. Riley or me know right away.

Dr. Raza Aly from UCSF. He's professor and

medical mycologist.

DR. ALY: My name is Raza Aly. I'm medical mycologist at the University of California-San Francisco. I'm here because I was invited by Novartis to give this talk, and I'm also being sponsored. The text of this proposal is done in conjunction with Novartis clinical team and myself. Therefore, the views are mutual, and also I'm part of the advisory panel for Novartis.

Since tinea capitis is infectious, so we propose active control. We're also proposing that the total duration due to disinfection should not exceed more than 10 to 16 weeks, the reason being because the patient drops out and loss of follow-up. And we also propose that active control, especially in a clinical trial, should be--the evaluator should be blind because exact matching griseofulvin control or its placebo with steady treatment or its control as far as dosage for appearance and taste is close to impossible. And compliance of double-dummy designs is also very difficult.

So diagnosis should be based on clinical presentation and culture methods. Minimal clinical score--I emphasize score--and positive KOH not required for entry. Key clinical criteria for diagnosis should be presence of black dot alopecia. Other signs and symptoms should be evaluated, but not required for entry due to variable

presentation of the disease. KOH in tinea capitis not required, since it produces a higher false negative.

The mycological assessments are culture considered as negative if no growth after 20 days of incubation. KOH evaluation is not required. Signs/symptoms expected to resolve within 12 weeks of study period, which are supposed to be cured erythema, papules, pustules, pruritus, on a scale of zero to 3. Zero is none and 3 is most severe.

Signs expected to improve but not necessarily resolved within 12 weeks of study period are black dot alopecia. At baseline, graded as present or absent required only for entry. Should be followed up by presence or absence of new hair growth. Scaling graded on a scale of zero, which is none, to 3, which is severe. Total sign and symptoms score based on those signs and symptoms that could resolve within 12 weeks are erythema, papule, pustule, and pruritus.

The second designs which are evaluated to be assessed, but not included on total sign and symptom score, as they are not reliable markers for success--these are scaling usually persists after mycological cure is documented. Alopecia will not completely resolve within 12 weeks, although new hair growth should be present. Lymphadenopathy, while generally presence in infection caused by Trichophyton, may be present even though patient

is cured, and the reason being because many of these patients have other respiratory infections.

Criteria to evaluate success are based on these: complete cure defined from evaluation of whole scalp and there should be no one target area. And these are negative culture: total sign/symptom score should be zero. These are erythema, papule, pustule and pruritus, and presence of new hair growth.

Since tinea capitis is an infection disease, we recommend placebo control not to be considered because it's unethical to use this. Griseofulvin is the only appropriate agent that is available in the U.S., so we have two choices regarding griseofulvin. Either we can use current practice dose or label dose, which is considered to be ineffective. Therefore, we propose that we should use current practice dose and this will avoid criticism that trial utilized ineffective doses of griseofulvin as a comparative agent, although no controlled studies demonstrated advantages or safety of this current practice.

Regarding concomitant treatment, study patients should use only neutral shampoo and hair care products. Use of antimycotic shampoo not standard in all practices. Use of antimycotic shampoo may complicate interpretation of mycological and clinical results.

Family household members should be screened for

culture whenever possible, but it should not be mandatory. Presence of carriers and infected household members should be documented. Treatment of carriers and infected persons other than study patients should be done outside the trial protocol. Only one patient per household should be allowed to enter trial to avoid problems with accidental switching of trial medications.

Tinea capitis due to Trichophyton tonsurans is now found in a number of countries outside of the U.S. Standard methods--we know that--for sensitivity testing are not that much reliable. So, therefore, we suggest or recommend that results from clinical trials conducted outside of the U.S. according to good clinical practice should be acceptable for registration of a drug within the U.S. if efficacy results grossly reflect those seen from U.S. centers.

Thank you very much.

DR. McGUIRE: Thank you, Dr. Aly.

At this point, we will go directly into the program. Dr. Ilona Frieden will speak on "Tinea Capitis: An Emerging Public Health Issue." And I should also introduce Dr. Paul Honig, from Children's Hospital in Philadelphia, who is here.

DR. FRIEDEN: Well, I want to thank Dr. Wilkin and the FDA for inviting me here today. And I'm so pleased that you think this is a sufficiently important clinical problem,

as many of us do, to have these hearings. I think it's one that has been kind of neglected because it doesn't cause death or very severe morbidity except in a rare group of patients.

But I became aware of the worldwide influence of the FDA recently. I was in Argentina a couple of weeks ago and the exhibit booths have these big posters and they say "Approvacado por FDA" [ph]. This is in South America, but it obviously means something worldwide when the FDA puts its seal of approval on an approach because you are so rigorous.

So I'm going to talk about the epidemiology and the scope of this problem in the United States primarily. In the first half of this century, there were very widespread epidemics of tinea capitis and it was considered a major public health problem. And these were due to Microsporum audouinii, and so public health nurses took Wood's lights and went through schools. And because this was a fluorescent tinea, it was not difficult to diagnose, though initially, because we did not have any antimycotic agents, it was rather hard to treat.

But with the advent of griseofulvin, and perhaps for other reasons as well, Microsporum audouinii seemed to fade from the landscape and is really a rare cause of tinea capitis in the present era. Then in the 1960s and '70s, Trichophyton tonsurans began to emerge as the major

pathogen. It's felt that this came through Central America and the Caribbean perhaps into the United States, coming up through Texas and then really spreading through large urban centers where it continues to have a major impact.

And if you look backward, this shift really began in the 1950s in a subtle, but there certainly was a period of time when many of us trained in the late '60s and early '70s when tinea capitis was a rather rare disease. And I saw only a few cases as a resident and one of the reasons I became interested in tinea capitis was that, as junior attending, I still thought of this as a rare disease. And I saw more and more of it and it was very fascinating to me to see such a rare disease over and over again until it dawned on me that it was no longer a rare disease, but that really piqued my interest.

This is work--and you can see these numbers because this is in San Francisco where I trained and this is work that Raza Aly, Mike Wilmington and I compiled and published showing--does anyone have a laser pointer--showing the type of dermatophytes infections produced by Trichophyton tonsurans in these three groups of the times periods 1974 to '78, '79 to '85, and '86 to '93.

And you can see that, proportionately, tinea capitis due to Trichophyton tonsurans compared to other causes increased and that numerically it increased quite

dramatically. And this was true of a number of other types of tinea, as well, perhaps as a sidelight of this that these, relatively speaking, increased in the later years.

But here we saw in this period when I was in training--actually, I was in medical school then, but in this period only 15 cases of tinea capitis due to T. tonsurans, and here 169. And in the United States currently, depending on where you are, these numbers are borne out, except in places where there are not large numbers of African American children, where Microsporum canis, the second most common cause of tinea capitis, is more prevalent--I shouldn't say more prevalent, but it's the more common etiology percentage-wise.

We do see Microsporum canis in the San Francisco Bay area and in other areas as well. It's spread by animals, usually cats, but it's not nearly as common a cause. But, again, depending on your population, it will range from, in Tucson, Arizona, to being the most common cause of tinea capitis, to, in certain inner-city populations, being only 1 to 5 percent of cases, so that the vast majority is really due to this organism Trichophyton tonsurans, an organism that is spread from person to person primarily.

So it is the major cause of tinea capitis, and now also in most areas the most common cause of tinea corporis.

It has been demonstrated in case series after case series to be more common in African Americans. Males and females are equally affected. The peak age is 4 to 6 years, but there is a wide spread beyond that peak age, so that you do see this infection in neonates occasionally, and it's not that rare to see that, usually getting it from a sibling or even a parent who's an asymptomatic carrier. You do see it in adults, and we continue to see Microsporum canis as well.

It's interesting, as Raza alluded to earlier, that there has been worldwide increase in Trichophyton tonsurans and that there have been cases and clusters of cases reported in England, in Canada, in Australia, and in Taiwan. These are mainly in patients of African dissent, but at least in Australia there are more patients of aboriginal dissent, and in Taiwan there really are no black individuals. So these are mostly Chinese-descent patients.

We did a few years ago a population-based study together with the California Department of Public Health, and this was a pharmacoepidemiologic study in which we used griseofulvin suspension as a surrogate marker for infection. And our rationale was that griseofulvin suspension is used in children. It's not used for very much besides tinea capitis because we don't tend to treat toenail infections in young children. They're not very common and even if they're there, we often defer treatment until these children are

older.

And there weren't too many other things that would have an impact on this data, and so we made the assumption that most, if not all, griseofulvin suspension use in California was due to tinea capitis. And then we looked at the California MediCal, which is the same as Medicaid, database from 1984 to 1993, which is a race- and age-based database, and also has the very nice characteristic of reflecting prescription use in an individual, so that if one individual got four prescriptions for griseofulvin in any one year, it would still only count as one time that they showed up in this database. So it happened to be a very nice, ready-made database.

And over that decade period of time, we see here a striking increase of griseofulvin prescriptions per 10,000 children, both in the zero to 5 years and the 5-to-9 years of age who were enrolled in our Medicaid program. If you break this down by race, which we were able to do with this database, you see that there was a statistically significant increase overall, as well as in white children, although it doesn't show up very well on this chart, but the numbers are very large and so the study had a lot of power, but a very striking increase in African American children in California. And this was true in both southern and northern California. It was somewhat more accentuated in northern

California.

So to summarize this in another way, the incident rate increased by 84.2 percent overall, with the greatest increase in African American children. In 1993, the end of the study period, the incident rates per 10,000 were 252 in African American, 23.1 if you took non-Hispanic white, and 17.5 Hispanic children. So the increased risk in African American children in a population-based study is 15-fold in this particular study, and that correlates well with other information.

But most of the other studies where they showed 93 percent of their patients were African American, you really needed to know what their clinic population was, and not all those studies tell you that. So this was really important data, we felt. And the rates we found were similar in boys and girls.

Additional supporting evidence that we found in California was that when we looked at ICD-9 codes, we did see increasing rates between about 35 and 51 percent in that 10-year period. This was a less dramatic rise, but this probably had to do with the fact that other codes, generic codes for tinea not otherwise specified were used, as well as the specific tinea capitis and tinea Baird code 110.0. We also looked at Kaiser griseofulvin suspension purchases, which increased from 19.3 per 10,000 to 80.3 in 1993, an

increase of 316 percent. There is some overlap because there is some Medicaid populations in the Kaiser system, but not a lot. But we weren't able to really separate that out, so there probably is some overlap of that data.

So I think I've demonstrated to you that this problem, least up until 1993, was certainly increasing fairly rapidly. My impression is I can't speak to the issue of increasing--whether we're continuing up that curve. I'm not sure that we are, but we certainly see plenty of tinea capitis in our practices, and the primary care physicians do as well.

I want to turn to another issue and that's the reservoir in the population. To remind you what a carrier state is, this is a person in apparent health who's infected by a pathogenic organism, in which in him or her there's no manifestations of disease, but which, when accidentally transferred to another, may produce an attack of a specific disease or the specific disease.

And the incidence of carriage of these organisms depends on the level of tinea capitis in the community. Or you might have to really put it another way. It may be that tinea capitis depends on the level of carriage, but it's a little hard to sort those things out. But if you look at population-based surveys, in Spain and Italy fairly recent surveys showed 0.2 percent, to an area with a very large

amount of tinea capitis due to an organism called Trichophyton violaceum in South Africa where 40-percent carriage rates have been detected. And this is again going into populations and culturing people who look like they have a healthy scalp and finding that they have the organism. In the United States, several studies have come up with an approximate 15-percent rate in African American school-age children. So these are sort of putting together a meta-analysis of several different studies.

If we look briefly at this issue of South Africa just to show that there is a potential for this problem to get worse, at least in some areas of the world, tinea capitis is felt to be endemic in this Cape Town area of South Africa. The carrier state there is felt to be a major contributory factor at the reservoir of infection and carriage was found in 41 percent of asymptomatic children, with persistent in 25 percent. So carriers obviously in some instances will revert to a culture-negative state without treatment necessarily.

These are some studies that I already alluded to which address this issue and come up with this around 15-percent rate, except for this study by Dennis Babel, who's in the audience, of a 30-percent rate in adult caretakers. And that may be more appropriate as a number within families as a carrier rate, and that was also shown in a study by

Vargo and Cohen.

So now if we look at the issue in adults, whom we don't think of as often having tinea capitis, Babel did report 30-percent asymptomatic carriage in adult caretakers. And this was a study from Israel with a 21-percent incidence in adult family members. And it's pretty clear from these and a few other studies that adults do probably represent a reservoir of infection within the family, as well as other children.

Addressing again this issue--and this is a study that Paul Honig was the senior author on and he may want to address this as well. But in this all-black parochial school in Philadelphia, this gets at some of the issues about asymptomatic and symptomatic carriage. And they found 3 percent of children in this school had symptomatic tinea capitis and 14 percent were asymptomatic. Fifty percent of positive cultures were from grades K and 1, so this 4-to-6-year-old group seems to be particularly vulnerable to infection.

They found sibling pair infections in a fair number of--almost a third of cases. They found no relationship to classroom seating, but clusters in playmates. Having young children in elementary school, I can tell you that often the playmates get seated separately so they don't create trouble, so probably that's the reason

the seating charts didn't--they deliberately put them in separate areas.

In any case, if you compare spore loads between asymptomatic and symptomatic cases, you find a direct correlation between the load of spores and whether or not you're actually overtly infected or not, so that there were a few asymptomatic carriers who had a lot of spores. And, in fact, when they went ahead and looked at these over a longer period of time, several of these ended up developing overt infection. But most of them had low levels of spore counts, whereas the index cases clearly had more spores. So it fits with what you would think would be the case.

The prognosis of carriage in this study showed that with a mean 2.5-month follow-up, 4 percent became overtly symptomatic and a large number remained culture-positive without treatment. Some of those, a minority, became culture-negative without treatment. So this can persist for a while and not all these children become overtly infected, but again they still may serve as a reservoir of infection.

Finally, just to mention the role of fomites, we know that viable fungi can be found on inanimate objects and potentially serve as a source of infection. But the scope of this is really uncertain, and it's really uncertain if environmental precautions are necessary or appropriate or

would make a difference; certainly, an area for further research.

And I do have two more slides. The mode of transmission, therefore, summarizing this, is clearly person-to-person transmission is probably primary. Fomites from combs, brushes, could play a role, and certainly asymptomatic carriage may serve as a reservoir of infection.

I want to bring up a question that we don't have an answer for in closing, and that is why would it be that tinea capitis occurs more in individuals of African descent. And the answer is we don't know. It's not an answer, but we really don't know. There have been a number of speculations in the literature and in conversations among those of us who are interested in this subject about hair care practices--pomades, traction, infrequent hair-washing.

The equal incidence in boys and girls makes the sort of pure hair care argument, I think, less compelling because boys and girls do take care of their hair in somewhat different ways. But it still may be an issue, and there are at least two studies that I know of, including one we're doing on a case control basis trying to look at this issue.

We do know that poorer communities and crowding have always been risk factors traditionally in tinea capitis epidemics, and these may well play a role in the current

setting. But beyond that, we don't really have a good handle on this.

Thank you.

DR. McGUIRE: Thanks, Dr. Frieden.

We're in pretty good shape for time, if anyone has a question you'd like to direct to Dr. Frieden.

Yes, Dr. Duvic?

DR. DUVIC: I have a question. I thought your data was really interesting, but I wanted to clarify a point. When you do cultures of skin in people who are asymptomatic, you call them carriage, not infection. I would say to you that they are infected, and what you call someone who's got an overt infection is someone who has manifested delayed hypersensitivity reaction to your fungal antigen and has immune response that manifests in erythema or scaling. The people that you call carriage may also be infected, but just not having developed that immune response yet. I'd like for you to clarify that.

DR. FRIEDEN: Well, as the Stedman's Medical Dictionary which I got the definition out of--I mean, I think there really is such a thing as someone who can carry an organism, if not necessarily this organism--strep, whatever, meningococcus--and not be truly infected--do you accept that concept sort of from a medical point of view?

DR. DUVIC: It depends on how you define things.

DR. FRIEDEN: Right. Well, there is a little controversy about definition of carriage in this infection, in that the group in England--Hay called those patients who have, I think, ten spores or more--

DR. HONIG: Less.

DR. FRIEDEN: Or less. They call those carriers, whereas those of us who look at children who look like they have completely healthy scalps--and you need to take a history to find out whether they have a completely healthy scalp, too. You can't just look. You have to find out whether or not they are using pomade to cover a scaly eruption in the scalp, which you can then not detect because it covers up scale, or whether or not their parents say, "No, they don't have scale on their scalp and we use pomade because this is how we're styling their hair."

So there is a subtlety to this sometimes, and that can confound the issue. But in children who have a completely healthy scalp and you culture this off of them, I would submit that we don't have evidence on a histologic basis. And they evidence that they spontaneously revert to negative cultures in a very high frequency would suggest that these children are not necessarily actively infected, but a segment of them probably are on their way to infection.

I think, just like you can carry this on a

telephone receiver, these spores can be viable on objects and not necessarily cause infection. And the immunologic response issue is an interesting one because we see a wide variety, as Sheila will talk about, at clinical manifestations. And the evidence is that the black dot tinea patients have very little in the way of immune response and that's why they have black dot tinea. And the people with kerion has a very brisk immunologic response and that's why they have kerion. But most of what we see is neither black dot nor kerion. It's this sort of seborrheic, scaly tinea capitis.

DR. FALLON-FRIEDLANDER: There is a precedent for the concept of carrier, too. How do we look at staphorius in the nares or micrococcus on the skin? So I think unless we show invasion of the hair shaft or actual disease, I find it hard to call it actual--it's not disease; it's just sitting there. And maybe we need to look at this better. I think all of us feel like no one has looked at the asymptomatic carriers histologically, looked at the hair shafts. But the data that we have thus far--I think we tend to think of it the way we look at nasopharyngeal carriage of staphorius or meningococcus, or micrococcus on the skin or staphepi [ph] on the skin.

DR. McGUIRE: Dr. Friedlander, and then Dr. Duvic, and then Dr. DiGiovanna, and then Dr. Miller.

Madeleine, it's yours.

DR. DUVIC: I just wanted to urge you as you collect your data to look at carriage rates and host response to carriage as clearly as you can. That's all.

DR. McGUIRE: Dr. DiGiovanna.

DR. DiGIOVANNA: Ilona, I have--

DR. FRIEDEN: Can I sit down?

DR. DiGIOVANNA: Sure.

Some dermatologists, and I wouldn't necessarily claim to be one, but some dermatologists have a difficult time getting positive cultures, or at least don't get a very high rate of positive cultures, and I wonder exactly what technique is used to determine the carrier state. How does one culture to determine that

DR. FALLON-FRIEDLANDER: We're going to talk about that later, or we can talk about it right now.

DR. DiGIOVANNA: I'll wait.

DR. McGUIRE: Let's wait.

Dr. Miller?

DR. MILLER: Ilona, would you comment on the reason the adults do not develop tinea capitis, why it seems to be limited to the pediatric population? Is that a correct statement or question?

DR. FRIEDEN: I think it's correct to say that it's much rarer in adults than it is in children, and I

think this was a I think, by, if I'm not mistaken, Stephen Rothman made that probably has to do with some kind of anti-fungal or fungistatic property of mature sebum that you would see in a post-adolescent individual. And that clinical observation which was made, you know, 50 years ago continues to stand as a valid observation.

But we certainly do see infection, and I think you see a little more infection when you get a lot of tinea capitis in a community. Then you're going to see a little bit more infection in the adults, but still they represent a small minority of what you actually see.

DR. MILLER: Is the infection--are we talking about just Trichophyton tonsurans or with the other dermatophytes, too?

DR. FRIEDEN: Well, we see it with other dermatophytes, too, but certainly in this setting--

DR. McGUIRE: At the time that Rothman was making his legendary collections of hair clippings in barber shops in Chicago, there wasn't much tonsurans around. It was all audouinii.

Dr. Aly?

DR. ALY: It used to be when we had tinea capitis due to Microsporum audouinii in generally kids, when they resolved puberty, it resolved on its own. And it was basically attributed to the sebum content, most likely fatty

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acids which are supposed to be anti-fungal and anti-microbial agents. For some reason, T. tonsurans--it's not really true about that because it generally does not resolve at puberty, as compared to Microsporum audouinii infection.

DR. McGUIRE: Dr. Honig?

DR. HONIG: Yes. I just wanted to mention, getting back to the carrier state, the only way that one could actually prove that the hairs were infected were to obtain a sample of hair, look at it and see if the spores are within the hair shaft. Unfortunately, in the asymptomatic individuals, which hair do you go after, because the ones that are nice and long and growing are not the ones that are infected and you can't tell if there's one or two in that maze, except if it were my head, that have broken off or have fallen off. So it's impossible.

DR. McGUIRE: Let's move on to Dr. Fallon-Friedlander's presentation.

DR. FALLON-FRIEDLANDER: Thank you for letting us get together and discuss this with you. I was asked to review the clinical presentations of tinea capitis, and felt that it wasn't unreasonable to liken it to some other great masqueraders that we have had over time. There's a little bit of overlap between my talk and Ilona's because I think you need some historical perspective to understand the difference in what we're dealing with now as opposed to the

1950s.

As Ilona told you, between 1900 and 1950, we had epidemics of Microsporum audouinii, again mainly affecting young caucasian pre-adolescent males. It was generally inflammatory disease with alopecia. The Wood's light evaluation was positive and it was very sensitive to griseofulvin. So, epidemiologically, it was an easier bug to deal with.

The gold standard there, what most patients who were infected had, they did have inflammation, scale and hair loss. It was easy for a nurse to go in and screen a population of school-age children. It was easy in the emergency room to see who was infected because they would fluoresce positive under Wood's lamp examination. And, again, it appeared that there were more epidemics of the disease rather than endemic disease.

And patients who were infected tended to die out after several months, whether they were treated or not, as opposed to the present. At the present time--and this has been an evolving picture, as Ilona mentioned. Notice, post-1950, particularly in the 1970s and '80s, now most of our cases, 95 to 96 percent of cases, are Trichophyton tonsurans, particularly in the case of urban disease. Again, Ilona told you we think it came from Mexico and Central America.

The vast majority of cases in the United States--and, again, I qualify that, the United States--are African Americans. Boys and girls get this disease. It is an endemic disease. There is a wide range of clinical presentations and that's one of the problems we have, the difficulties in making the diagnosis. As Ilona has elaborated on, the asymptomatic carrier state, we believe, is a significant problem in transmission of this disease. And, again, we can't use the Wood's lamp to make the diagnosis.

I was going to spend a minute to talk about what do I mean about Microsporum audouinii was very sensitive to griseofulvin and the bug we have now isn't. If you look in the PDR and if you look in references, people are still listing very low doses for treatment with griseofulvin. However, if you go out and talk to pediatricians, to the people who are taking care of patients, they are not using the PDR reference.

And, in fact, we do have some legitimacy in the doses we're using in that the American Academy of Pediatrics publishes a red book which is a report on the Committee of Infectious Diseases of the American Academy of Pediatrics, and they have, in fact, over the years really changed their stand on how much drug we should be using.

And as you can see, in 1974, 10 milligrams per

kilogram was enough. Things have been inching up, until recently, in 1997, they not only increased the dose, but they also put all of these modifiers on about how you may need to treat longer, you may need to use higher doses. And they do mention that treatment with either itraconazole or terbinafine is effective, but again not FDA-approved. And Boni Elewski will go into this in further detail maybe this afternoon.

So let's talk about clinical manifestations. Sometimes, it's real easy. As one of my mentors would say, even the elevator operator could make this diagnosis. We've got our target site. We have scale. We can't see as much inflammation and black skin, but it's there in this child, and we have broken hairs or what we would call black dot tinea. So sometimes it still is quite easy to make the diagnosis. And, again, just another close-up of this child and there are shorter hairs within this area of involvement than the rest of his scalp.

However, there are times when it is not as clear-cut and there are many variable pictures. Now, another classic picture that we have is that of the kerion, which is a tender, boggy mass. And I could say that that's straightforward and even the elevator operator would make that diagnosis, but I have at least two cases a year in my hospital where these children are sent to the OR to be

drained as scalp abscesses. So people still make the mistake and think that these are bacterial infections.

But, really, the bigger problem is in the more indolent cases, cases where it's a little more subtle. And some patients with tinea now will have a picture that really looks a lot like folliculitis. They may or may not have hair loss. They can have black dot or gray patch presentations, and in that case it's a little bit easier. They can have alopecia that is non-inflammatory, and then the big problem for us now is that they can have a picture that looks very similar to seborrheic dermatitis where they will have scale, they will have no erythema, and they will have no hair loss. And, again, we have elaborated on the issue of the asymptomatic carrier state.

So here's a picture of a kerion. Again, you have a boggy mass underneath this hyperkeriotic scale, and for most dermatologists we can do just fine making this diagnosis, but general pediatricians--generalists still sometimes believe this is a bacterial abscess. I put this slide in just to remember to spend a moment on Microsporum canis, but I think that Ilona did a very nice job of explaining that in this country Microsporum canis is not the major problem. The major problem at this time is Trichophyton tonsurans.

T. tonsurans is spread from person to person and

Microsporum canis is usually spread--even though the name is canis, it's usually cats who are the transmitting agents. But if you ever wondered how, in fact, people could get infected, this is a person in my office who loves her animals dearly and clearly has close contact with them.

Other examples of clinical manifestations: here's a kerion, a boggy mass where we actually have exudate and honey-crusted scale on the surface, which brings up the issue of co-infection with bacteria. And Paul Honig has done a lot of very good work on this issue and, in fact, you can culture bacteria out of kerions. What difference this makes in the course of the disease isn't clear-cut. Paul's work has shown that if you treat patients with antibiotics, as well as antifungals, you won't get a significantly different outcome in their final course.

So we know that you can get bacteria within these lesions, but for the most part patients will clear on griseofulvin alone. Some people do add prednisone to treatment, but again it's not clear-cut from the data that thus far has been published that it makes a big difference for the majority of patients.

Another example of a kerion, and you can see where people get confused and think of the issue of bacteria because you can have a massive amount of honey-colored crust, as well as sometimes some hemorrhagic crust. Now,

we're getting into pictures where you can see that things are getting a little more difficult because you have hair loss, but you may not always see clear-cut areas of erythema, especially in black patients. You do have scale in this case. There are cases where you won't have that.

And here's a case where a patient presents and for all the world looks like a bacterial folliculitis, erythematous and, in fact, has fungal disease of the scalp. Now, some would say that the more erythematous--the more inflammation you have, the more acute the infection, the more likely it is that it's Microsporum canis. And I am not going to go into that in great detail. I don't believe that you can make the distinction on a clinical examination. I don't believe that even KOH can make that distinction for most practicing physicians.

I can make the distinction on ectothrix versus endothrix which will help me characterize it, and Denny Babel is actually going to discuss that with you. But for your average physician out practicing in the population, they cannot make that distinction on examination and they must wait for fungal culture results.

And, again, another example. For all the world, you know, it looks like a bacterial process. We have pus there. But, in fact, it is tinea capitis. Here's an example of a girl who was first thought to have traction

folliculitis because she presented with red follicles around the hair shaft and her mother braided her hair very tightly. But, in fact, over time it became more clear-cut that she had tinea capitis.

And another example where you could see where the first doctor might have thought it was a traction folliculitis from all the braiding that occurs and the traction on the hair. But, in fact, over time hair loss developed and on culture it proved to be tinea capitis.

Non-inflammatory alopecia. You used to be able to tell residents that that was alopecia areata, probably. You can't do that anymore. This is the case of a girl who was referred in to us after she had been treated with interlesional steroids for months for presumed alopecia areata, and she, in fact, had Microsporum canis.

Another example. But this is the real problem for us now and this is a case of a child who comes in and for all the world looks like he has seborrheic dermatitis. He has greasy scale, he has no hair loss and he has diffuse greasy scale. And, in fact, when you culture him, he will grow out Trichophyton tonsurans, and this is something that generalists still aren't aware of.

So how do we make the distinction between seborrheic dermatitis and tinea capitis? Well, there are some clinical clues which we try to impress upon the

residents who are training with us and one of them is looking at the rest of the skin. Obviously, if somebody has a spot of tinea corporis, you might think that, in fact, there's something on their head as well.

Another hint is cervical adenopathy, and in this slide I think you can see--I'm not having a lot of luck with my pointer, but I think you can see that she has adenopathy as well. And in this example again, you see this patient has adenopathy. You need to look for that always when you're trying to make the diagnosis.

And another associated finding is the ID or autoexczematization reaction which doesn't show well on photograph, but this is a child who was first treated with some topical steroid lotions because he was thought to have seb derm, then progressed, then was treated with topical antifungals. Finally, somebody realized he needed systemics. His mother thought he was on his way to cure and then he developed this itchy generalized eruption that looked like eczema and, in fact, was what we call an autoexczematization reaction and does not represent allergy to the medication but rather a hypersensitivity reaction.

So, again, just to review, we try to teach people to look for cervical and occipital adenopathy. If there's an autoexczematization reaction, you need to think about it and you need to look at other family members who may be

infected.

Documenting the diagnosis, fungal culture is the gold standard. KOH is helpful in the right hands, but has a higher false positive rate. And though I try to teach my residents to learn how to do it well, what I most impress upon them is that I want them to send cultures to make the diagnosis. Adenopathy and response to therapy are helpful in distinguishing seb derm-like cases from the carrier state. But, Madeleine, as you've pointed out, sometimes it's really hard to know exactly do we have infection or do we just have carrier.

How do we best test for the presence of fungus in the scalp? There are several issues in pre-school children. One is what can we do that will keep them in one place at one time? If we do things that are traumatic to them, they may not come back for follow-up and in anyone who has done studies on tinea capitis, that is a major problem. There is an incredible drop-out rate for patients and if you're traumatizing them the first time they see you, they will not be back.

In our office, we have used a simple Q-tip or cotton swab moistened with regular water. We roll it over a large area of the scalp and plate it out on DTM. I have just completed a study where I've taken these samples, just transferred them out of the office in regular, routine

culturette tubes. Because of insurance issues, I now am not allowed to culture on DTM in my office for many insurance plans because they want it sent to a central lab where it can be done cheaper.

And, in fact, we've found 100-percent concordance. Not only is this method concordant with a toothbrush and plucking, but you can also send this sample out of your office. It can sit around for days and you will still get positive results, and I think that's consistent with Hebert's work and others who have shown that the fomites can live for a long time.

So, John, you were asking what is the best way to do this. I believe that the cotton swab is absolutely the best both in terms of sensitivity and also in terms of compliance and getting patients back. This doesn't bother the kids; they think it's cute, it's fun. So, that's what we recommend.

DR. DiGIOVANNA: Excuse me. You use that both for culturing a patient with an active lesion and also for determining the carrier state

DR. FALLON-FRIEDLANDER: Yes, and you do not need to get hairs in this Q-tip, the cotton swab. You need to have it wet and you need to survey. I try to survey a reasonable portion of the scalp, and you're picking up the fomites with scale. You don't need to have any plus parts.

Yes?

DR. MILLER: Are you going over just the hair or do you also go to the scalp with the Q-tip?

DR. FALLON-FRIEDLANDER: The scalp is key. That's where I'm trying to sample from. I'm sampling from the scalp.

DR. MILLER: You're going to the scalp.

DR. FALLON-FRIEDLANDER: Yes, the scalp and, you know, vigorous rubbing, but nothing traumatic, nothing that would bother the patient.

And just another example of the wet Q-tip. Many people have asked me does it need to be sterile. In fact, it appears that it doesn't need to be sterile. We haven't had problems with contamination.

Differential diagnosis, why this is so important. There are lots of diseases that can look like tinea capitis and this makes it very hard on the generalist in terms of determining what's going on; again, atopic derm, seb derm, psoriasis, traction folliculitis.

How are we doing for time?

DR. McGUIRE: We're fine

DR. FALLON-FRIEDLANDER: I'd spend just a few more minutes. Again, Ilona raised the issue of the asymptomatic carrier state, and along with that I'd like to raise the issue of the importance of looking at family members. When

I was growing up, they used to say the family that prays together stays together, and now we say the family that stays together gets tinea together

And I think this is a good example. Here's a family where the index case is on your left, and if anyone would bother to look at mom, they can see that she has two papules on her arm, on the upper part of her arm. And the brother there, in fact, when he was cultured, cultured out Trichophyton tonsurans as well. Another example of a child who came in with clear-cut tinea capitis, and mom has clear-cut tinea corporis.

So, again, to reiterate some of the things that Ilona has said, Denny Babel did look at adult household carriers in families with an index case. And look at the incidence of positive cultures, 30 percent. The asymptomatic carrier rate among siblings of index cases, 63 percent in a study done by Vargo and Cohen, in Pittsburgh. However, the background rate there was high, 15 percent in the asymptomatic rate in controls. In that same study, they found that 48 percent of families with an index case had at least one other person with a positive culture.

Now, if we compare this to random asymptomatic children in a pediatric clinic in Missouri, a study that was done by Sharma, she found a 4-percent incidence of the carrier state. But it's interesting. Her study included

100 caucasian children and 100 blacks, and the incidence in the black children, in black females, was 8 percent of the asymptomatic carrier state.

So what I would posit to you is that we all believe that the family area is a very important one in terms of people being infected and possible sources of re-infection and possible sources of transmission of disease. And Ilona has very nicely reviewed Williams' and Honig's work. I'm not going to beat that to death.

The 13-percent asymptomatic carrier rate was for Trichophyton tonsurans. If you included Microsporum, it was 14 percent, and again these high numbers, people who are culture-positive in the group study. But, again, the important thing that I think Paul tried to emphasize in this study is that when they looked at siblings and close playmates, that's where an extremely high incidence of infection or the carrier state occurred, so that we need to deal with the family members and close playmates. We need to take as much or more time with that group as with the classroom setting.

So, in summary, tinea capitis is now in the United States caused predominately by Trichophyton tonsurans. It affects mainly school-age black children. There are a variety of clinical presentations, making it harder for us to identify those who are infected. And the asymptomatic

carrier state, we believe, plays a significant role in transmission of disease.

Thank you.

DR. McGUIRE: Thanks very much.

We're doing pretty well for time. Unless there are one or two burning questions, I'd like to go on into Dr. Dennis Babel's talk.

Either you or Sheila, what is the longest duration that you have followed an asymptomatic carrier, somebody that you thought was not clinically infected? Do you think that any of them convert to clinical disease after three months, six months, a year?

DR. HONIG: Yes.

DR. McGUIRE: Is that going to be in your talk?

DR. HONIG: I have a slide that's going to show that.

DR. McGUIRE: Okay. Let's wait until your talk.

DR. HONIG: And in our study, one or two did convert from carrier to--

DR. McGUIRE: Don't let the cat out of the bag.

DR. HONIG: Okay.

DR. FRIEDEN: Can I make a comment to what--well, just two subjects that came up in Sheila's talk that I think we need to come back to. One is in terms of what Raza Aly has talked about in terms of trying to design a study. One

is the issue of whether we see black dots in all these patients, and we need to definitely discuss that because as Sheila said, and my own impression is that we have patients where we really don't see what we can identify as alopecia or the black dots.

And the second is the issue of the autoexczematization, so-called ID reaction, how that is going to be dealt with when we look at the issue of possible toxicity of drugs, because it's such a common problem we need to be careful about looking at this issues.

DR. McGUIRE: And it's misleading.

DR. HONIG: Just one other thing. The only thing I would disagree with what Sheila said--in the kids who have the seborrheic type of tinea capitis, in most of those, although the physician cannot clinically perceive hair loss, if you ask the parents if they think their child has lost hair, I would say 90 percent say yes.

DR. McGUIRE: Okay. Dr. Babel?

DR. BABEL: Thank you. Dr. Wilkin, thank you so much for bringing us all together. This is a very essential area of work and it has been a long time coming. We appreciate it.

You need to know that Tracy Riley, when she called me to invite me, made a point of telling me that I had to limit my presentation to 20 minutes. I guess she realizes

how long-winded us mycologists can be, so I promised her that I would be succinct.

What I'd like to address is specifically the mycology, the organisms which can cause disease, and really how to acquire a specimen; if we're going to set up clinical trials, how best to prove that indeed we have an infectious process and what organism is causing it.

Relative to our dermatophytes, about 43 species worldwide, a dozen of which can cause human disease, practically speaking maybe half a dozen in North America, but how many of them really contribute to tinea capitis? Fall into three different genera, but what's their reservoir?

We do have some strains which normally reside in the soil and they can cause a very inflammatory tinea capitis. Those that are zoophilic--and we've addressed Microsporum canis--can be harbored by various animal hosts, principally cats and dogs. And, of course, our main pathogen, the parasite tonsurans being anthropophilic, normally resides in a human host and it really cannot reproduce outside the human host. Even if we set up animal models, we have to severely immunosuppress those models to get Trichophyton tonsurans to grow.

What we have noted is, generally speaking, if we deal with anthropophilic species, they tend to cause the

less inflammatory processes. Eighty percent of our T. tonsurans tinea capitis will be more the low-grade, chronic type of infection. Some of them do go on to give us folliculitis, give us a separate and boggy kerion. Those acquired from animals, those from the soil--usually, they're considered more antigenic. They usually cause a more inflammatory disease.

Different forms of tinea capitis and how do we acquire specimen? With our gray-path ringworm caused by Microsporum audouinii, this organism was anthropophilic, so it had a human host, the human environment. The bulk of these youngsters would develop well-defined areas of alopecia, and normally you could recover organism within that area of alopecia. Usually, all of the hairs within that lesion were infected and that's one of the distinguishing features. That's how we're going to separate that from tonsurans.

Black dot tinea capitis caused by Trichophyton tonsurans. We can have diffuse areas of involvement. I think the picture that we've really seen today is tremendous variation in clinical presentation of this disease. That's why it's hard to assess. What criteria do we use to empanel a patient in a clinical trial? If it can range from absolute limited alopecia with a little bit of scale to a God-awful separate of boggy kerion, you know, where do we

draw the line? What criteria do we use?

Those that do become more inflammatory more frequently a zoophilic or geophilic species. And one other form of disease seen in this country--it's uncommon and probably will not be included in any clinical trials, but it's a real burden to that particular patient group--is the Favus.

Let's take a look at endothrix versus ectothrix. This is one of the pictures that we'll see in direct microscopy. When the infection is initiated, the fungal unit itself grows down the hair follicle in the form of hyphae and actually penetrates the hair at Adamson's fringe. For the most part, dermatophytes cannot live in viable tissue, so this is the keratinizing portion of the hair.

And it keeps pace with the growth of the hair, so the fungus grows downward, but never broaches that Adamson's fringe. And, of course, it's subsequently carried up with that infected hair. If it disarticulates, if those hyphae separate into erythrokinidea [ph] within the hair, it's an endothrix. And this particular clinical presentation is the one that we see with black dot tinea capitis, with our T. tonsurans infections.

If, on the other hand, the hyphae separate into erythrokinidea on the very surface of the hair, we'll wind up with a little bit different picture. We'll get

destruction of the cuticle, and usually in many cases we'll have the production of a fungal metabolite called teradine [ph]. These youngsters will fluoresce. We can take a Wood's lamp and their scalps will fluoresce. So we have seen a changing epidemiology. Trichophyton tonsurans does not fluoresce. This tool doesn't help us in the diagnosis of this disease.

Let's consider the endothrix invaders, and really in North America the key organism is Trichophyton tonsurans. Trichophyton tonsurans probably came to this country from the western Mediterranean, came in, colonized Central America and Mexico; with the demise or the disappearance of Microsporum audouinii, began to move up through the southern states and now is the major contributor to tinea capitis in the United States and Canada. Trichophyton violaceum is really Europe's answer to T. tonsurans, causing a very similar form of tinea capitis.

These three organisms--Trichophyton sudanense, gourvillii and yaoundii--are pretty much restricted to the African continent, to Western Africa, equatorial Africa, where they cause very similar disease, this endothrix type disease. Unlikely that we'll see these agents in North America. On occasion, we do pick up a violaceum. Trichophyton schoenleinii, I suppose, technically is an endothrix. That's that organism that causes Favus and we'll

take a look at that in a moment.

So how do we obtain specimen? Classic black dot tinea capitis, or at least a textbook description of black dot tinea capitis--we seldom see it with this clear a presentation. What's happening is our infected hairs are weakened because of the keratinase produced by the dermatophyte. So they curl, they break off at the follicular orifice. And if you're lucky, you'll clearly visualize these little black dots. Because of the curling, sometimes they're sub-cuticular. You may have to actually scrape these to get them out. They'll be a little bit deeper.

So what about collection of specimens, inoculation of media? Well, I personally feel it's essential to clean the area that you're going to sample, the reason being many times the parents, the caregivers, are going to put some sort of vaseline, some sort of lotion on there to diminish the scaling. And, indeed, putting a vaseline, an oil of some sort does seem to diminish the scale, but it makes it more difficult to acquire a quality specimen, especially if one's going to consider direct microscopy. So I feel it's ideal to clean that area first.

We then would like to scrape scale. If we can visualize black dots, those are ideal. If we had the fluorescent form of tinea capitis where we have little hair

stubs, they literally can be plucked because they tend to extend 2 to 3 millimeters above the scalp surface. Unacceptable specimens--and this is important--are long hairs. By definition, long hairs are not infected. If they were, they would be weakened; they'd break, they wouldn't be long.

Hair clippings, long hairs, tend to contain bacteria. So if we directly inoculate a culture system, we may wind up--even with inhibitory media, we may wind up with bacterial colonization, and certainly we'll begin to minimize our ability to isolate the pathogen that we're looking for. The ideal media for fungal isolation will be one with inhibitors, so that could be Saboraud's dextrose Ager with chloramphenicol to inhibit bacterial contamination, cycloheximide to inhibit fungal saprophytes. Trade names for this product would be Mycocel or Mycobiotic Ager.

So let's obtain a specimen here. We're going to clean the area first with an alcohol swab. Many different tools are available. What's most comfortable in your hand? We've heard reference to the culturettes, the swabs. They're ideal, they do a good job. If one is doing a KOH, you have to be aware that on occasion you're going to get cotton fibers in that KOH and if you're not careful, you may misinterpret that, consider that to be a hyphae. But it's a

good source of specimen, absolutely.

So in addition to our cotton swabs, we have toothbrushes, we have scalpel blades. Some clinicians prefer using a glass slide. They'll take the edge of that glass slide, scrape the area of alopecia and collect material. All acceptable. I personally prefer the Bard-Parker blade, especially if my black dots are subcuticular, but the toothbrush works well. We brush it through the area of alopecia, impress it right on the Ager itself and ultimately we can isolate the organism.

For KOH exam, I like to gather material, smear it on the glass slide, and then add one of a number of various solutions for direct microscopy. I personally prefer 20-percent KOH of dimethyl sulfoxide. It simply works more quickly. But any of these solutions can be quite acceptable.

Now, what about consideration of KOH? We've heard that the KOHs have limited sensitivity. And I think that's correct, the reason being the skill of the individual doing this procedure can vary a bit simply based on training and experience. However, KOH exams have a very high specificity because if we literally collect one of those dark hairs, we can see the organism in action. We can see its pathogenicity. There's absolutely no question that the organism is contributing to that disease.

The culture, on the other hand, has a much greater sensitivity. We can gather material from the scalp, grow the organism all day long, but is that organism pathogen or is it a contaminate? Well, if we add the clinical presentation of disease, I think we can assume that it's a pathogen. So, bottom line, for clinical trials I suppose culture would be the gold standard, would be the best way to go. We may have more difficulty getting solid data points with KOH exam.

I'd like to present a few different presentations of black dot tinea capitis and how I would acquire specimen in these situations. Here, we have limited alopecia. There is some scaling. I would simply go into this area, clean it, scrape it. Disease can be quite extensive with significant hair loss. Once again, anywhere within these areas of alopecia, ideally we could isolate organism.

What we need to know is, within the areas of involvement, not all hairs are involved. With Microsporum audouinii, the old gray-patch ringworm, virtually every hair follicle within that lesion would be involved. With our black dot tinea capitis, it randomly selects different hair follicles. So we're going to look for the broken-off ones. We're going to scrape those surface areas to collect material. If they are not visible, if we have dense scaling in that area of alopecia, we simply clean it and scrape the

scale. We really don't have to visualize black dots.

What about the more inflammatory presentation? Well, this gets tougher. It's hard to collect good material here. If I were to scrape some of these lesions, get that purulent exudate, I could make a smear. I could do a Gram's stain and maybe see organism. That would be tough. If I had a PAS stain, I really could visualize it, but that's not practical for the front-line physician.

Better yet, let's go peripheral where it's a little bit less inflammatory. If we go out here into the area of alopecia and scrape, we can probably recover organism quite readily. Where it gets real tough are with these nasty kerions, these diseases that are allowed to go on. They're left untreated. These youngsters develop these God-awful masses on the scalp. Sometimes, we have to remove this material and go underneath to collect specimen for culture.

Here's what we're looking for ideally with our black dot tinea capitis. If one is doing a KOH, you'll collect a fragment of hair, and characteristically the hyphae will separate into erythrokinidea. With our black dot tinea capitis, these erythrokinidea are large; they're 5 to 7 microns. We're going to visualize them under low power, 10X. So we can scan a field. If we happen to get a nice fragment of hair, we should be able to perceive these.

And, of course, the fungus is elaborating its enzymes. It's going to really break down that hair, dissolve the keratin fibrils, and eventually the whole hair simply disintegrates. You can see the little melanin granules in the background here and you can see how much larger the fungus is and simply spilling out of the hair.

In our organism, Trichophyton tonsurans, there are three or four different strains of tonsurans. It's felt that this particular strain, Trichophyton tonsurans, variety selferium [ph], is a little bit more aggressive, is more likely to lead to kerion formation; Trichophyton violaceum, Europe's answer to Trichophyton tonsurans, a very characteristic colony, but seldom seen in this country.

Well, what about those that are acquired from animals? And I'd like to introduce Budweiser; he's my love dog. He is not harboring the organism, but certainly many animals can; in the case of Microsporum canis, cats, dogs, horses and monkeys, but most frequently kittens. Other animals which can harbor organism that can lead to tinea capitis in North America include Trichophyton verricosum, carried by cows. If we happen to live in a more rural community where we have farm animals, they are a consideration, but the incidence is much lower. So on the animal, it can be apparent disease. Many times, it can be inapparent, especially in kittens, little white flecks on

the nose, hard to pick up, although the vets are pretty good at this.

Clinical disease in the patient tends to be extremely inflammatory almost from the get-go. One tool that we can use to help separate this animal-acquired infection from the T. tonsurans, the human-acquired infection, is the Wood's lamp. So we'll put this patient in a darkened room, fluoresce their scalp, and either we'll see specific pinpoints of light, those individual hair follicles which are involved, or actually the whole area of alopecia will fluoresce a bright blue-green. We can sometimes select the specific infected hairs and use those for culture, and here you can see the fluorescing hairs on a culture plate itself.

What dermatophytes are capable of causing a fluorescent tinea capitis? Well, the old Microsporum audouinii which contributed so much disease to this country, and it has now disappeared; Microsporum canis acquired from animals; Microsporum canis, variety distortum. In this country, we will occasionally see this organism. It's usually associated with monkeys that have been imported from South America, but an uncommon cause of disease.

Microsporum ferrugineum causes a fluorescent tinea capitis in Asia, and in this country we'll see it in youngsters in Hawaii and occasionally, with migration, we'll

pick it up off of patients in the continental United States. Trichophyton schoenleinii--that's that oddball one, the one that causes Favus--also fluoresces, but it's a different type of fluorescence. Instead of the bright blue-green, it's more of a dull gray fluorescence.

Here's what a KOH would look like from the Microsporum canis. It's a small-spored ectothrix, little tiny erythrokinidea in almost a mosaic tile pattern, much harder to perceive. This is one that you're going to miss under low power unless you're really thinking of it.

So we'll scan. The organism is coating the entire surface of the hair. This separation of hyphae in erythrokinidea is associated with that metabolite production, teradine, which gives us that bright blue-green fluorescence. Fairly easy to isolate the organism. They grow quite readily. Gather material and put it on a culture system; they grow fairly rapidly. This white, hairy Microsporum canis, very early colonies, and eventually they develop the characteristic yellow-orange pigmentation.

Lastly, Favus. Just to be complete, this disease is seen in North America. The organism is endemic in Eastern Europe and the Balkans. It's endemic in Iran. And when we had all the immigration at the turn of the century, immigrants that were coming in through Ellis Island were prevented from coming into this country if they Favus, which

is a very characteristic, very apparent disease seen from childhood through adulthood. It doesn't go away on its own unless it's treated.

We wind up with a permanent scaring alopecia, the formation of scutula, sort of cup-shaped structures that are composed of hyphae and cellular debris. Actually, it's probably one of the very first fungal diseases to appear in the medical literature. Around 30 A.D., a medical writer, an author by the name of Allus Celsus, wrote about this Favus presentation. And the therapy of the day was rather interesting back then. All they had available was tar, so they would take this tar, this pitch, and work it into the scalp, the area of involvement, led it harden, let it sit there for about a couple of weeks, and then the patient would return to the physician and this sort of pitch helmet would be forcefully ripped off the scalp, epilating the hair. And apparently it was quite effective therapy because there was usually very few return visits, but a very destructive disease. In this country, most cases are seen in Kentucky, rural Appalachia. It tends to run in families. It tends to be passed from one generation to the next.

And, really, those are the organisms that we see with greatest frequency in this country and I'd be more than happy to answer any questions that you may have about their isolation or address any other issues.

Please.

DR. McGUIRE: Dr. Miller?

DR. MILLER: Would you comment on why we don't see much Trichophyton violaceum in the States if it's so ubiquitous in Europe, you know, with travel and what not?

DR. BABEL: Maybe it's a matter of filling a niche. Microsporum audouinii, which was so prevalent in the '40s and '50s through the mid-'60s, took up that space, caused all that clinical disease. And then it disappeared and no one knows why. There are some rather interesting theories, one of them being in the late '60s the commercially available shampoos started using a new wetting agent, and supposedly Microsporum audouinii was very sensitive to that wetting agent, so maybe that was one reason for the disappearance of that organism.

But in the void that was left, Trichophyton tonsurans moved up, was readily available, was down there in Mexico and Central America. So it simply was available and filled that space. Why don't we see T. violaceum here? Probably because it's simply not that readily available. It's a matter of what's there, what's our biggest reservoir, and at this point in time its tonsurans.

What I think is more curious is why it's so specific for black Americans or patients of African descent. And we theorize cultural things--hair dressings, different

habits like that. That may be a small part of the issue. I think it's something bigger, though. Remember, our dermatophytes have the ability to live on keratin, which is a very complex scleroprotein, and I personally think that maybe we have a difference in keratin among individuals. And organisms which elaborate the keratinases are able to deal with some individuals more readily than others. So it may be keratin composition, and once again that's probably just a small part of the big picture.

DR. McGUIRE: Dr. Aly?

DR. ALY: Dennis, my impression was that T. violaceum is the most predominant organism in Southeast Asia, such as Pakistan, India and those regions, than in Europe. And I don't know. Somebody said why is it so prevalent in Europe.

DR. BABEL: From the reading that I've done, it's very common in the eastern Mediterranean versus the western Mediterranean. We see it causing disease in Africa and it is seen throughout Europe, but you're right, and also does cause disease in Asia.

DR. ALY: Because in India and Pakistan, 90 percent of the tinea capitis is due to T. violaceum.

DR. BABEL: Yes, T. violaceum. Thank you.

DR. McGUIRE: Okay, thank you.

DR. BABEL: Thank you.

DR. McGUIRE: Dr. Elewski?

DR. ELEWSKI: Thank you, Mr. Chairman, and I would also like to thank Jonathan Wilkin for inviting me. And I will be talking about therapy, so I will give a conflict of interest statement. I have received funding for clinical research and/or speakers bureau from the four companies whose products I will discuss, namely Novartis, Jantzen, Pfizer and Ortho. That is my conflict of interest. So I actually have quite an in-depth presentation planned and very little time, so I'll try to do the best to keep on time. We'll be talking about current therapies of tinea capitis, looking at what's used now and off-label.

When treating children, the patient benefit versus the risk of drug adverse events is probably the most important consideration, which is why for just about everything besides tinea capitis and onychomycosis, a topical therapy is given for childhood mycotic infections. Griseofulvin has been the standard treatment for the past several decades.

Looking at objectives of tinea capitis therapy, there are really two. One is treatment of the organism from the hair follicle to cure symptoms, and the second is to eradicate the organism from the hair shaft and follicle to prevent relapse and epidemic spread. In order to do this, you need to have an oral drug, and fortunately for our

patients we have several different oral drugs to choose from--ketoconazole, itraconazole, fluconazole, terbinafine and griseofulvin.

These drugs all work at different parts of the fungus. The majority of these targets are ergosterol synthesis. This would include the azoles and the allylamines. Griseofulvin is different. It works at the nuclear level. It works by inhibiting micro tubal formation. The azoles and the allylamines work at the level of the ergosterol, which is the key sterol in fungal cell membrane, but they work differently, as you see from this slide.

This is griseofulvin. Let's begin first with the product that we've been using and is currently FDA-approved. Griseofulvin has been the drug of choice for dermatophyte infection since it was approved in 1958. It is very well-tolerated. There are certain problems that need to be addressed. One is it's poorly absorbed from the GI tract, and it's absorbed best with food. There are micronized and ultramicronized preparations which display better absorption.

Side effects are minimal. The drug is fairly well-tolerated in children. It should be taken with food, as I've already addressed. Other side effects that occur are headache, GI disturbance, and then occasionally some

laboratory phenomena such as leukopenia, neutropenia, have been reported. Fever, epistaxis are other side effects, very, very rare.

What is currently used now in the PDR? In the PDR, the recommended dose is 5 milligrams per pound per day, or about 11 milligrams per kilogram. That's the approved therapy. The duration is six to eight weeks. Now, this dose is not really used, nor is recommended by pediatric dermatologists or mycologists. The suggested therapy is more like 15 to 20 milligrams per kilogram per day of the microsize formula, which may need to be increased to 25 milligrams per kilogram per day, and the duration is 6 to 8 weeks or longer. I usually treat eight weeks or more. With the microsize formula, 20 milligrams per kilogram per day is a dose that I start at. If you use the ultramicrosize tablets, a dose of 15 milligrams per kilogram per day can be used.

This has already been briefly mentioned, but the Red Book report on the Committee on the Control of Infectious Disease historically looking at the doses that have been recommended, in 1974 a dose of 10 milligrams per day was recommended, with up to 10 to 20 milligrams per kilogram per day in 1994 and also in 1997. And some children may require higher dosages.

But also keep in mind that for the past several

decades, the organisms have changed. Thirty years ago--Microsporum audouinii was very common 30 to 40 years ago, which was when griseofulvin first came out and became approved for this indication. Now, we don't see M. audouinii in the United States. The organism that we see is Trichophyton tonsurans. So although the dose has been changed, we're also treating a different infection, so that's very important to keep in mind.

And unlike other mycotic infections such as tinea pedis where it's predominately one organism, T. rubrum, tinea capitis can be caused by a variety of organisms. And when you treat a patient, you need to know what the organism is because you may need to select your drug based on the organism, and also select the duration of therapy based on what the organism is, as I will say in just a few moments.

So to summarize the treatment of tinea capitis, you need an oral therapy. Griseofulvin is the gold standard. The dose that is currently used, but not recommended, is 15 to 25 milligrams per kilogram per day, and the duration is 8 to 12 weeks.

To summarize griseofulvin, I think it's a safe drug. It is available in a liquid formula. I don't think the liquid formula is that convenient for our patients, though. The liquid formula comes in a four-ounce bottle. The bottle is 125 milligrams per teaspoon. So if you are

treating a 20-kilogram child and you're using the dose of 20 milligrams per kilogram per day, that child needs 16 ml's of griseofulvin a day to get 400 milligrams, 20 times 20.

So they go through one four-ounce bottle in about a week, and with managed care now that one bottle doesn't last long, a week, so you have to order four bottles at once for a month's supply. And many of these patients don't go back to keep getting the prescription renewed. And another problem is the managed care company may not permit four bottles to be dispensed at baseline visit. Other disadvantages of griseofulvin are we're seeing treatment failures. This may be due to drug resistance. I think compliance is another big reason for treatment failures.

Now, there are patients who require an alternative to griseofulvin--allergy to griseofulvin, intolerance to griseofulvin, and non-responsiveness to griseofulvin. Let's briefly look at these.

This is a patient I saw in my office in Cleveland. He did not respond at 25 milligrams per kilograms per day, but most of these patients who do not respond really want a lower dose and typically you can continue to up the dose of griseofulvin until you hit a dose that the patient will respond to. Sometimes, you can do that. Sometimes, it doesn't work.

Patients who are, quote, unquote, "allergic" to

griseofulvin may not really be allergic to griseofulvin. They may have the ID reaction. The ID reaction generally presents as lichenoid papules that start at the scalp and work its way down. It can be differentiated from a drug eruption by the appearance of the skin, but these patients are not allergic. This is some hypersensitivity response.

So now let's look into the other methods, the newer methods or off-label methods of treating tinea capitis. First, let's write down a wish list. What is the ideal drug for a child with tinea capitis? One that would be a liquid formula that would taste good, that would be effective, that can be given for a month or less with no adverse effects. But does that drug exist? And the answer is no.

We have four drugs to choose from. Besides griseofulvin, we have ketoconazole, itraconazole, fluconazole and terbinafine. Problems with these drugs are, one, there's very few pediatric oral formulations. And, two, we really don't know the pharmacokinetics of these drugs in children.

Ketoconazole I'm not going to say a lot about. I do not recommend it for tinea capitis because of the liver toxicity that can occur. So given the fact we have other drugs, I'm going to omit ketoconazole from our discussion. Furthermore, there's no liquid formula and you would need to

do laboratory monitoring.

Itraconazole is the next drug on the list. This is the formula of itraconazole. The first study was done by Bob LeGendre. He looked at 50 children under 10. They had either M. canis or T. tonsurans. He treated them for 30 days and he had a 90-percent mycologic cure rate. I published a study in 1994 looking at three children with T. tonsurans tinea capitis who failed griseofulvin. This was an open-label study. Thirty days was the course of treatment. I cured all my three patients and they were no side effects.

Based on that study, I was referred dozens and dozens of patients who had failed griseofulvin or could not tolerate griseofulvin, and I subsequently published this. We at that time had over 120 children. I published 120 children who had failed griseofulvin, but were successfully treated with itraconazole. The dose I used I tried to keep between 3 to 5 milligrams per kilogram per day, and I treated everyone 4 to 6 weeks. Everyone was cured eventually and I had no one who discontinued therapy due to adverse events.

The problem with itraconazole is the fact that it's available in a capsule and it's hard to administer a capsule to children. And furthermore the problem is that you can't precisely dose with a capsule. You can't cut it

in half like you could a tablet to come out with the precise 5 milligrams per kilogram per day. So I have complicated dosing regimen where I may give one capsule or one every other day or two some days, depending on the body weight of the child.

This is a child who failed griseofulvin who was successfully treated with itraconazole. This is a kerion. This was due to T. tonsurans. And this child I saw for several months prior to starting the child on itraconazole. Whenever I saw him, I would wake up depressed, knowing I would see him, because I was running out of options, and he responded nicely to itraconazole. This is an adult who had extensive tinea capitis, extending also down into her neck. She also responded to itraconazole and she had failed griseofulvin.

Potentially, you can pulse itraconazole. It has a reservoir effect. Again, the pharmacokinetics are not that well-known in the hair, but there have been a couple of authors who have written about the pulse using a pulse with two weeks drug-free interval, not three, as we use in onychomycosis, but two, followed by a second pulse with two more weeks drug-free, followed by a third pulse.

Dr. Gupta published a paper in the British Journal of Dermatology. He had ten children. He treated them at 5 milligrams per kilogram per day one week, two weeks off, and

one, two and three pulses cured one, six and three patients. And he had no adverse events. He actually eventually studied 15 children totally, had a 100-percent cure rate, and one-third, or 5 out of 15, required 3 pulses.

Now, there was one paper that was published in March of this year in the Journal of the American Academy of Dermatology looking at itraconazole in children that did not look so promising. They published 25 patients who completed the study. They were between 1.5 and 11 years. They used a dose of 100 milligrams per day for 4 weeks, along with agivant therapy with selenium sulfide shampoo, and they had a cure rate of only 40 percent.

Now, I can't really explain these results. There were 29 patients additionally who started the study that dropped out or were lost to follow-up, and furthermore the authors used the same dose, 100 milligrams per day, for all of these children rather than varying the dose according to body weight. So, that might explain some of the lower results than you might expect, plus they treated for only four weeks, not four to six weeks.

There is also a solution of itraconazole, but I'm going to just use a couple minutes to tell you why I'm not recommending it for use in children at this point. There is one poster that looked at the safety of it. It was a poster in 1996 at the ICAAC meeting, which is a major infectious

disease meeting. They had three groups of eight children of varying age. They concluded that for 2 weeks, a dose of 5 milligrams per kilogram per day was safe and effective. But they used a duration of only two weeks and it was a poster.

The problem with the solution is that it contains cyclodextrin, and from my perusal of the PDR that has been reported with pancreatic adenoma in rats with human exposure dosages. Now, that's why I'm not advocating it right now for the use in children, the liquid formula, which is different than a capsule.

So to summarize itraconazole, it's an effective drug. It has a good safety profile. We need more controlled studies and there's no suitable liquid formula.

Let's move on to terbinafine. This is terbinafine. It's an allylamine. There's been several reports on the safety of terbinafine in children. This report came from Dr. Jones and was published in the BJD. He looked at 196 children who took terbinafine. There were 22 adverse events. They took terbinafine for a variety of reasons, not just tinea capitis. There were 22 adverse events in 15 patients, but in only 6 of these 15 patients were the adverse event related to drug therapy, and 3 of these, or half, were due to stomach or GI disturbances.

There was another published study in the British Journal of Clinical Pharmacology called the PMS study, and

in this study, which was a post-marketing surveillance study 82 children, 82--less than 12 were included and they received terbinafine for a variety of fungal infections and there was no increase of adverse events in children as compared to adults. So those are two papers showing the safety of terbinafine in children.

There is some data on the pharmacokinetics of terbinafine looking at children as compared to adults. Based on the pharmacokinetics, there is a dosing range that is recommended. What is currently recommended is for those people greater than 40 kilograms, a dose of 250 milligrams a day; for those between 20 and 40 kilograms, 125 milligrams; and for those less than 20 kilograms, 62.5 milligrams a day. The big question is how long do you need to treat with terbinafine, so let me just spend a few minutes reviewing this literature.

The first study came from Pakistan by Dr. Haroon. It was an open-label study. He had ten children; nine of them had T. violaceum and one was T. tonsurans. He treated everyone for six weeks and he varied the dose according to body weight. He cured everyone in this study and there were no side effects.

The next published report was by Dr. Jones of 105 patients and it was study comparing four weeks of terbinafine versus eight weeks of griseofulvin. In this

study, 85 percent of the children had T. violaceum and 3 had T. tonsurans. The results showed that 4 weeks of terbinafine, looking at week 8 and week 12, was comparable to 8 weeks of griseofulvin. So the author concluded that four weeks is sufficient for therapy. But keep in mind that the infections in this study and the previous study was Trichophyton tonsurans or Trichophyton violaceum, predominantly.

There was a poster at the 1997 AAD meeting looking at terbinafine in tinea capitis by Dr. Krafchik, in Canada. She had 40 patients. It was an open-label study. She also varied the dose according to body weight and she treated them for two weeks. The predominant organism was T. tonsurans. There was, as you can see, one M. canis and one T. sudanense. What she found was that 39 out of 40 children were cured with two weeks. The one child who was not cured had Microsporum canis.

Dr. Haroon also published a study looking at one week of treatment, versus two, versus four weeks in children. Again, there were a variety of organisms. The majority were T. violaceum or T. tonsurans; 3 percent had M. canis. There were over 50 patients in each of the 3 groups for 1 week, 2 weeks or 4 weeks, and final evaluation was at week 12. These are the results. Four-week had an 86-percent mycological cure; 1-week, 74 percent; and 2 weeks,

80 percent.

So, as you can see, you had a higher cure rate with increasing duration of therapy, but there was no significant difference in cure rates between one and four weeks. And also adverse events did not seem to differ based on the duration of therapy. And he concluded that although four weeks was superior to one, one week was probably effective.

So to summarize terbinafine, it's an effective drug against dermatophytes. It has a good safety profile. There's quite a bit of published data available, but there's no U.S. controlled study and there is no liquid formulation.

Next, fluconazole. This is the last drug we'll discuss. This is fluconazole. It is a triazole. There is some pharmacokinetic data on fluconazole in children. Fluconazole has been given extensively to young neonates and premies for systemic use, I.V. for children with systemic mycotic infections. So the pharmacokinetics have been looked at at a variety of dosages, 2 milligrams per kilogram and 8 milligrams per kilogram. There is a liquid formulation which actually tastes pretty good, and the drug is approved for children over 6 months, but not for this indication.

The first published study of fluconazole in tinea capitis came in the Lancet and it was a one single-case

report of a child who was given fluconazole for 20 days and was cured. A two-month follow-up showed no recurrence. Based on this study, investigators in New York entered 41 patients into a dose-finding study comparing 1.5 versus 3 versus 6 milligrams per kilogram per day, treating these children for 20 days.

Cure rates were higher as you increased the dose, and at 6 milligrams per kilogram per day, the cure rate was 89 percent, and this paper was subsequently published in the JAAD about one year ago. And these authors concluded that 6 milligrams per kilogram per day for 20 days was sufficient with fluconazole.

I published a paper looking at 12 children between 3 and 12. All 12 of our children had T. tonsurans. We used 5 milligrams per kilogram per day. We could give it precisely because we used either the liquid or the tablet formulation, and all 12 of our children were cured. We treated everyone for six weeks and they were culture-negative by week four. But I didn't know that, so we continued treatment until week six.

There was also a poster that was published by Dr. Montero-Gei in Costa Rica, and he had 20 children with tinea capitis and he administered the drug once weekly at 8 milligrams per kilogram once weekly. Now, the majority of these children had Microsporum canis, which is different

than we see in the U.S. And he treated them four to eight weeks and everyone was either clinically improved or cured by week four, though some children, he felt, needed to be treated up to eight weeks.

So to summarize fluconazole, there is a liquid formula available. It is effective. It has a good safety profile, but we just don't have a lot of data and a lot of studies.

So now I just would like to end with a discussion of cost of what's currently available because you can't really discuss treatment without adding cost to the equation. My table shows the dose, the milligram per kilogram, the dose per day, the milliliters or milligrams needed per day, the number of days of treatment, and the total dose. And I'm going to go right to part two of the table which discusses the cost.

Griseofulvin, assuming an eight-week course of treatment using a liquid formula, would cost about $170. If you treat 12 weeks, the cost will be $228. Itraconazole, using the capsules--and this is for a 20-kilogram child; all of this was calculated for a 20-kilogram child. Using a 30-day model, the cost would be about $140.

With fluconazole, using either the tablets or the liquid, the cost varied between $150 to $170. Terbinafine, for a 20-kilogram child, the cost was actually the least.

If you treat for 4 weeks, a 20-kilogram child would need 14 tablets, 125 milligrams a day. So the cost was $78 or, for 2 weeks, $40. So it was the cheapest and actually cheaper than griseofulvin. All the others are about in the same ball park as griseofulvin. And this does not take into account failures. It does not take into account blood monitoring; if indicated, visits to physicians, et cetera. It's just the cost of the drug.

So to summarize our treatment, all these drugs are very effective for tinea capitis. Griseofulvin is still our drug of choice because it is what is currently approved, but if the patient cannot tolerate or fails griseofulvin, we fortunately have options for our patients.

Thank you.

DR. McGUIRE: Thank you.

The audience has been sitting for two hours and I think that we should break for a few minutes and come back and have questions for Dr. Elewski and hear from Paul Honig. So we're broken again and we will get back together at 3:15.

[Recess.]

DR. McGUIRE: The last talk of the session before the Committee discussion will be given by Dr. Paul Honig, "Topical Adjunctive Therapy to Reduce Contagion."

Start whenever you're ready.

DR. HONIG: Okay. My topic is that of adjunctive

therapy after griseofulvin has been started or any other medication has been started. I think what you've gotten from the speakers today thus far is that T. tonsurans is the most common organism that produces tinea capitis in the United States. The incidence of the infection is increasing and spread can occur either in school, within families, or from animals.

If you look in the American Academy of Pediatrics recommendations, the Red Book, you'll see that they recommend that children not be kept out of school. The sentence that follows this paragraph says, "However, adjunctive therapy is advisable," and they mentioned selenium sulfide.

You've heard that spread occurs in schools. If you look at some of the studies, they show essentially that if you have an index patient in a classroom, the asymptomatic carrier rate seems to increase. With no index cases, the asymptomatic carrier rate decreases and sometimes disappears.

The study that we did that has already been mentioned several times was a semi-quantitative study, and I think if you look at all of the studies, all two or three that have been done on the use of adjunctive therapy, you will find that there is no quantitative aspect to those studies at all. And what we already know is that if you're

an asymptomatic carrier that has a low colonization rate, 50 percent of the time you will lose the positivity of the culture within a 2- to 5-month period. So is it the medication that's causing the negative culture or shampoo or what have you, or is it the natural course of loss of these spores? I think that's very important to keep in mind as we discuss adjunctive therapy.

In our particular study in this school, we showed, as opposed to the others, that if you looked in the classrooms where there were index cases and also looked at the asymptomatic carrier rate, when you eliminated the index cases, the asymptomatic carrier rates actually increased. And what that meant to us was that maybe school isn't that important a place to acquire infection, but maybe it's the family setting.

And then here we go with some more of these pictures of multiple siblings within a family, and my favorite picture is this one, the four kids with the positive cultures all from one family. So family spread, I think, is very, very important, and eliminating the infection is next to impossible because of family spread and compliance and if you look at studies, you can see.

In this particular study, a lot of the sibs and adults are infected and these are studies where there's an index patient within the family unit. Here again, they talk

about adult carriers are present in a majority of the cases where children have tinea capitis. And if we go on and on, you can see that the adults and sibs do acquire the infection within the family setting.

So the problem is that of containment of the infection. And, before, you had asked the question how long can these asymptomatic carrier rates last. Well, more importantly was the fact that we found that even if you started treatment with appropriate antifungal medications, you continue to get positive cultures for up to eight weeks after treatment was started and the child looks cured. The asymptomatic carrier rate--if you look in varying studies, there can be persistence in anywhere from 10 to 25 percent of the cases for up to 6 weeks, up to 8 months.

So we're talking about a problem that I don't think has been perpetuated by the fact that we don't have the proper antibiotic or antifungal agent, but more we don't know how to contain the infection. We don't know the epidemiology as well as we should and we don't know the characteristics of the organisms.

In any event, due to the fact that we're finding the positive cultures despite antifungal therapy, we started to look--and James Laden did these studies with Ken McGinley--at varying preparations that might be used, in addition to griseofulvin, to eliminate the positive

cultures. And they looked at things such as coal tar, salicylic acid, or sulphur, selenium sulfide or zinc parathion in varying concentrations.

And these are the reciprocals of the dilution and what they used was dilutions that were weaker than is available commercially in shampoos and they found that these--I should go back. They found that selenium sulfide and coal tar, as well as zinc parathion, had an effect in eliminating positive cultures, and this was done in vitro.

So we then tried to do a study where we looked at children who were infected with tinea capitis, were started on griseofulvin, and then in one group had a bland shampoo added, clotrimazole twice daily or selenium sulfide twice weekly. These were the number of individuals with positive in each of the subsets, and these were the number that continued to have positive culture two weeks after therapy. And you can see, with griseofulvin, all ten were positive with griseofulvin alone, and there were some that were positive up to eight weeks out.

If you looked at adding a bland shampoo, six were still positive at two weeks and two were positive at three weeks, and those two never came back for the eight-week culture. Compliance is a major issue and something I'd like to emphasize. Whenever you need to treat with a medication for six to eight weeks, you can imagine how successful that

is, especially when those of us who are pediatricians or infectious disease individuals know that with a strep throat where ten days of penicillin is important to complete, maybe seven days out of the ten days of treatment are completed in a majority of the cases. So compliance is a major issue. The longer you treat for, forget it.

In any event, when we tried clotrimazole in addition, 12 were still positive and 3 were positive out to 4 weeks. With selenium sulfide shampoo biweekly--and this is a 2.5-percent preparation--1 was positive at 2 weeks and 15 were negative. The one that was positive stayed positive until four weeks.

Now, there have been other studies. This is a study from South Africa where they looked--and what you have to keep in mind is these studies, again, were not semi-quantitative. They didn't look at colony counts at all. The organism here was T. violaceum and these were asymptomatic carriers that they treated rather than infected individuals.

So what they did is if they were going to use the econazole preparation, they looked at those with positive cultures and those who had clinical findings who they assumed were infected. And if they didn't have clinical findings, they were assumed to be a carrier. And they used selenium sulfide 2.5 percent, povidone-iodine, and a

control, which was baby shampoo.

And what was interesting also in this study--for some reason, they only took the females and put them in the selenium. I don't know whether that was designed to prove that selenium sulfide didn't work or what, but you'll also see that this was the group that there were the least number that completed the study. And what they showed is that povidone-iodine worked the best for T. violaceum in infected individuals as opposed to the other preparations.

Now, a Kuwaiti study looked at M. canis and they used a dose of griseofulvin of 10 milligrams per kilo per day M. canis, and what they found was that if you used griseofulvin alone, if you cultured it 4, 6, 8, and 10 weeks out, you would find--and there were 20 individuals in each subset--you would find that it took 10 weeks to get a negative culture when there was no adjunctive therapy used.

With selenium sulfide for M. canis, it was no better than griseofulvin alone. With topical ketoconazole applied once daily, it took eight weeks for clearing, and with topical clotrimazole twice daily, it took six weeks for complete cure and negative cultures.

Now, we talk about 2.5-percent selenium sulfide shampoo. Well, that's a prescription item and maybe if this was over-the-counter, there would be some benefit. So someone decided to compare 1-percent and 2.5-percent

selenium sulfide shampoo. All the organisms were T. tonsurans. The dose was appropriate and they did biweekly shampoos using the 2.5-percent Selsun shampoo, 1-percent Selsun, and a control. And what they showed was at 2 weeks, 2 of 12--and there was a lot of drop-out in some cases, as you will see--2 of 12 were negative. One of 18 in the 1-percent was negative, and none of the controls.

At 4 weeks, 2.5-percent, 70 percent of the patients were now negative, a little less than 50 percent in the 1-percent, none of the controls. At six weeks, things got even better, except for the controls, and by eight weeks there were negative cultures. So you started to see some improvement by four weeks and they felt that 2.5-percent was no better than 1-percent selenium shampoo.

Now, as far as animals are concerned, because animals play a role in the spread of some of these infections, some veterinarians in this particular journal decided to take hairs from infected animals and either soak them or shampoo the hairs--and I'm not exactly sure how they shampooed the hairs, but these were hairs that were cut from the animal--and kept them in these varying preparations for five minutes each, either shampooing or soaking, and found that lime sulfur and enilconazole required only two treatments before the cultures in these animal hairs became negative. Chlorhexadine and povidone-iodine--we've seen

that before--took four treatments, and sodium hypochlorite and ketoconazole took eight treatments. And what Captan is didn't work. So there are studies that the vets do that may be helpful for us as well.

So what I can tell you is that although we talk about adjunctive therapy, there are really no really good studies that have used semi-quantitative culturing to really prove that a medication, a shampoo, or what have you works really well. And so we've got a problem because we continue to have positive cultures, despite the fact that the child is clinically healed.

And that is my story.

DR. McGUIRE: Let's turn some attention toward Dr. Honig's talk, and then we didn't have discussion after Dr. Elewski's talk. Does anyone have questions for Dr. Honig?

Go ahead, Madeleine.

DR. DUVIC: I just wondered if there was any data on some of the more potent topical antifungals as agivants, such as Lamicil or the gel products that might be able to penetrate down into the hair follicle a little better.

DR. HONIG: There may be, but I've not been able to find them. If anyone else knows of any studies--personally, I doubt there are. Selenium sulfide was used mainly because of its staying power. Even though you rinse the hair, the preparation adheres to the hair shafts and

scalp, despite rinsing, and it is cidal. So, that's why we tried using that one as opposed to others.

DR. McGUIRE: Fred, did you have a question?

DR. MILLER: Yes. Is there a problem with relapse in the children who have been treated, but they remain carriers? Do you see that happen or not, and are they more likely to relapse and get the disease as opposed to the person who--is there a difference between them and the person who is just a carrier who doesn't seem to get the disease?

DR. HONIG: That's a great question because some of the what we call resistance may actually be reinfection rather than relapse. Remember, we've all been mentioning the fact that there are a lot of individuals within family units who are infected and maybe they are providing the source for reinfection, or possibly the fomites that are in this household. We have no idea how to get rid of the fomite problem or eliminate the spread from individuals who are infected.

I tried to do a study where we would try and figure out how to handle the asymptomatic carriers. Our IRB would not allow us to use a medicine in an asymptomatic carrier. No way any IRB is going to allow that to be done, so it's going to be a tough question to answer.

DR. MILLER: And currently, if you have a child

with tinea capitis, do you culture the other people in the household to see if they are indeed carriers?

DR. HONIG: What we generally do is, by history, we ask if anyone is symptomatic within the family unit. If they are not, we don't do anything. If we find that an individual whom we are treating cannot be cleared of their infection, we then ask the family to bring the entire family in, which is not always successful, and then we culture everyone to see if there is a source for this problem.

DR. MILLER: And then if they're positive, what do you do to eradicate it then?

DR. HONIG: If they're clinically positive, then we start treatment with oral medication. If they are asymptomatic carriers, we use 2.5-percent Selsun shampoo.

DR. McGUIRE: Dr. Frieden?

DR. FRIEDEN: I just wanted to mention sort of a couple other real-world problems because I think, ideally, you'd culture everyone in the family. We don't do that. Who would pay for those cultures, for one thing, if we did them? So we wait. In the bounce-back patients, we do what Dr. Honig just said.

The problem--and, you know, it gets to the heart of your question, Dr. Miller--is that in real life what happens is the patient starts to get better. And in my experience, in the indolent cases, which is the vast

majority, as soon as their symptoms start to go away, they don't come back for a follow-up appointment because it's not that bad of a problem at that point and you've been giving them these prolonged therapies and then that's it. You don't see them until six months later they come in and you don't know whether they ever got rid of the infection. In ideal life, you'd like to reculture them at the end to make sure they're negative once they're a month off therapy, but that only happens in a minority of cases.

The other real-life problem, though, you have if you want to include topical shampoos in your regimen is compliance for frequent shampooing because in black patients, we really need to try and figure out how to get to the issue of whether or not everyone is really doing this at a uniform rate because I get a lot of feedback that twice-a-week shampooing is really impractical. It's really not necessary in other circumstances and it's not done, I think, very frequently. So if you build something like that into a trial where the compliance rate is extremely low, you may just be adding a really big confounding variable.

DR. McGUIRE: Ilona, you're getting near a point that is very dear to me, which is that your idea of a shampoo may be entirely different--I'm sure it is--than Paul Honig's idea of a shampoo. People expect a lot of a--you expect more of a shampoo than you do any other topical

medication. Most people get in the shower, put the shampoo on, rinse it out and think that they have shampooed. Very few people think about the duration or the length of time that the shampoo is in contact with the scalp or the hair. The number of times per week, I think, is not nearly as big a variable as the duration of time that the shampoo is in contact with the hair or scalp.

Paul, I wanted to ask you one question. I probably missed it, but you showed data on griseofulvin plus selenium sulfide and different concentrations of selenium sulfide. I didn't see the combination of griseofulvin plus zinc parathion.

DR. HONIG: That was not studied.

DR. McGUIRE: You'd expect that to be even better than the selenium sulfide.

DR. HONIG: Possibly. We went with what Dr. Laden suggested we do because he was the one that did the original in vitro studies. The other comment about frequency of shampooing--the guys will shampoo twice a week, no problem. But if you ask a female to shampoo twice a week, they'll look at you like you're crazy. And we've had some of our African American residents talk to their fellow residents about different ways of management of hair and we asked the patients themselves and average frequency of shampooing in females is once every two weeks. So there is an issue and a

problem as well, unless we could get a shampoo that lasted for a long period of time.

DR. McGUIRE: I posited the question about progression from pure carrier state to clinical infection. Is there any way that you can measure the movement of individuals from carrier state to clinical infection; that is, can someone remain a carrier, have positive or measurable spore numbers, and then sometime down the line have clinical infection?

DR. HONIG: The answer is yes. When we did our study in this parochial school with 224 total patients, of the children that had a four-plus spore count, one--I think it was only one, actually--one became infected, clinically infected. All the others did not. We followed the patients anywhere from two to five months after initial cultures. So some of those kids were cultured two months down the line. We were doing the cultures over a period of 16 months, about, and I think we cultured the school 4 different times.

DR. DUVIC: How do you define infection?

DR. HONIG: Again, only by clinical findings, scaling, hair loss, inflammation, pustules, whatever.

DR. McGUIRE: Dr. Friedlander, you had a question, I believe.

DR. FALLON-FRIEDLANDER: I just wanted to reconfirm what Paul is saying about treatment. For African

Americans, using these agents actually damages their hair. It dries their hair out and they will not be compliant. I mean, for a lot of them it really does--it's so drying that they don't want to use it, and that's our highest population who needs treatment. And I've had the same experience where they'll look at me and nod and then say you can't be serious about it.

The other thing is, I think, Madeleine's point about how do you define infection. It's really hard now, and sometimes it's sort of--you could say it's almost retrospective. You have some kids who have greasy scale. They don't have hair loss that you can discern. Maybe you can get a history from mom, but you can't discern it, but they have lymph nodes. You treat them and they get better. Their lymph nodes go down, their scale goes away. So that's an odd way to define disease which is not the right way and it's one of the problems we have.

DR. McGUIRE: Dr. McNeil, do you have any views from the CDC or any questions from the CDC that you'd like to put on the table?

DR. McNEIL: I think, you know, we're certainly very interested in this burden of disease, and I was speaking to some of the people earlier before the meeting. Of course, it's very difficult for us to look for traditional sources of funding within CDC to study this

because we're competing with diseases that cause a lot more morbidity and mortality.

But I think, trying to be resourceful, we have tried to identify databases and I think this has occurred now. I think Dr. Frieden sort of started this and there are databases that will enable us to at least get some general impression of the epidemiology of this condition--physicians' offices, visits, the National Ambulatory Medical Care Survey. There's also emergency room physician databases.

And, you know, preliminary evaluation of those databases that we've presented as a poster last year at the Infectious Disease Society meeting--we actually confirmed some of the findings of Dr. Frieden, and this certainly seems to be a problem in African American children, particularly in the ages 4 to 6.

DR. McGUIRE: Well, I'm glad you came. It did occur to me that Dr. Wilkin had invited you to proselytize you, but I--

[Laughter.]

DR. McGUIRE: Anything is possible.

Do you have a question?

DR. ALTAIE: This is Sousan Altaie, FDA. I have a question for Dr. Honig. When you defined the carrier state having less than ten spores--

DR. HONIG: I did. That's the Hayes definition of less than ten spores.

DR. ALTAIE: Per what? What is the unit, what is the background on that?

DR. HONIG: See, what most people do is take a particular area of the scalp, rub the area with whatever, toothbrush, Q-tip, for a certain period of time and then streak it out on a plate, then look to see the number of colonies that are growing on that plate. The unit itself I cannot tell you, but all I can tell you is that the English consider anything above ten colonies as infectious, whether there is clinical evidence of infection or not. Our definition is it doesn't matter how many spores are there; we have to see some clinical evidence of infection.

DR. ALTAIE: Right. Microbiologically, to me, really it's sample size-related. You could take a huge scrape off a carrier and end up with more than ten and call it an infection.

DR. HONIG: Yes, but we take a well-defined area that we're working in. We don't just sample the whole scalp.

DR. McGUIRE: Dr. Duvic?

DR. DUVIC: I had a question for Dr. Honig. Your data in the classroom showed that as the index case was treated, the number of carriers went up, and you interpreted

it to be non-classroom. I would say that another way of interpreting that data might be that it takes a while to establish a carrier state in a classroom. You may have one spore on a child initially as a classroom contact. It may take a month before four children show enough spores to be carrier state. So I don't think your data necessarily precludes classroom transmission.

Secondly, what do you tell these children about hairbrush treatment because, to me, that's the major fomite possibility? Is that done in the study?

The third issue is it seems to me that the carrier state may depend on frequency of hair-washing and that may impact your epidemiology findings. And you could do a correlation coefficient between number of times people wash their hair per week and carrier state or something.

DR. HONIG: Yes, that has been shown to be true that if you wash your hair more frequently--there was this one study that looked at different kinds of hair care, and hair greases didn't make a difference between the boys and the young ladies. And washing the hair, which is done more frequently by the guys, showed that there was less incidence of infection. This is not carrier state now.

As to your first comment, we had seating charts from the teachers to see where the asymptomatic cases and asymptomatic carriers were to see if the kids around them

were more likely to become carriers and this did not prove to be true.

DR. DUVIC: What about sharing hats or hairbrushes?

DR. HONIG: Well, we didn't do all of that stuff.

DR. McGUIRE: Some of the panel members have to leave to catch planes and trains. We'll have a last question from Dr. Aly.

DR. ALY: I was just wondering how long these erythrospores of T. tonsurans remain viable, particularly on fomites? Is there any study to show that

DR. FALLON-FRIEDLANDER: Didn't Adelaide at Baird look at that?

DR. HONIG: She just looked to see if they were there or not.

DR. ALY: Not on a patient, in inanimate objects.

DR. HONIG: All she did was--Dr. Adelaide at Baird just looked at different--cultured various things in the household, including telephone, I think, and sheets and pillow cases and dolls and toys. And it was just either--it was positive or negative. She didn't say whether we watched--they didn't track out how long they were positive for.

DR. McGUIRE: Okay. DODAC has posed some questions for us. We have six questions, yes, nothing on

the back of that page.

Number one, which clinical subtypes of tinea capitis should be studied and should any subtypes--e.g., with kerion--be excluded for the indication, tinea capitis?

Dr. Wilkin, do you mean studied or treated?

DR. WILKIN: Well, treated and studied. I guess I think of them pretty much the same way. In other words, four years ago when we had our Advisory Committee to consider onychomycosis, just as an example, we went over the different clinical presentations of onychomycosis and it was thought that the proximal subungual and the superficial white variety really didn't need to be studied, that the distal subungual would be sufficient for the indication onychomycosis, but then, by convention, that would not apply to canderal [ph] onychomycosis. So it's a similar question here. What clinical subtypes, black dot only, black dot plus other subtypes, should be looked at?

DR. McGUIRE: Okay. Well, let me put the major subtypes out here and then have the Advisory Committee add or take away, and I would say the typical black dot. I would not exclude kerion. I would include the seborrheic dermatitis form, the folliculitis form, as well as the--did I mention the alopecia areata form, the one without the inflammation? So I would include all the major clinical subtypes.

Now, would any of the Committee like to remove some?

Dr. Elewski?

DR. ELEWSKI: I totally agree with what you said. I think all these types should be included. I would probably exclude Favus, if anyone had a Favus. I don't think it occurs in the U.S., but it is a subtype of tinea capitis. So I would exclude that because it's going to be harder to treat, if that would occur.

DR. McGUIRE: If anybody has a Favus, they're going to call you, of course.

DR. ELEWSKI: They can call me. I'll be very excited. I'll come over personally.

But black dot tinea capitis refers to black dots breaking off at the scalp and if someone has blonde hairs, they're going to have blonde dots. If they're going to have red hairs, they have red dots. So limiting a study to black dot tinea capitis limits it to a population of patients.

DR. McGUIRE: Okay. Endothrix.

DR. ELEWSKI: Yes, or black patients with black hair. So I think you really--to be, you know, fair, you have to look at all the types, inflammatory types as well as non-inflammatory types.

DR. McGUIRE: Okay.

John?

DR. DiGIOVANNA: This is more a question to the experts. With most of the therapies that are used, does a kerion require greater or longer therapy than the standard tinea capitis of all the other types? And if so, wouldn't that make it a little more difficult to show efficacy for a standard treatment, and for that reason shouldn't it be sub-

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DR. McGUIRE: Dr. Honig wants to answer that.

DR. HONIG: Yes, yes. I would have excluded kerions as well, for two reasons. Number one, they're difficult to treat. Number two, in the area of the kerion, frequently the culture goes negative due to the inflammatory response of the host. So it depends on whether they have other areas of involvement, which they frequently can have but sometimes don't. So I think that sort of makes things a little more difficult in deciding when you've got a cure.

DR. McGUIRE: Okay. Let me try this out on you. I would include kerion because it's a big part of the practice and you'd be excluding a lot of kids if you excluded it. And you would have to stratify it; you would have to indicate that these children had kerion and these children didn't. But I think it's--

DR. HONIG: Well, that's okay.

DR. McGUIRE: And, you know, is it an inflammatory response, an immune-driven response? I have this very

confused notion that at one end of the spectrum is kerion and at the other end of the spectrum are all of the papular lesions and red lesions that we see scattered on the trunk. I see them on the palms, between the fingers, and sometimes on the scalp. I can't tell where one reaction stops and the other begins. But let's hear from some experts.

Dr. Babel?

DR. BABEL: One of the problems that we face with kerion is a standard of care might be the concurrent use of corticosteroids to reduce the inflammation, to minimize scarring. In a clinical trial, you're not going to be allowed to use immunosuppressive agents and on that basis we would have to exclude patients with kerion if indeed the standard of care is to use anti-inflammatory agents to--

DR. McGUIRE: Well, then I would urge that there be another arm in that study.

DR. FRIEDEN: Could I--

DR. McGUIRE: Yes, Dr. Frieden.

DR. FRIEDEN: I think clinically what we see are two different things, very rare, and I think perhaps we should consider for exclusion, are solitary, intensely boggy, tumor-like plaques which are the ones that become abscesses and are the ones that end up inadvertently going to the OR to be drained before we ever see them.

And then we see children who have boggy areas

within a field of more scaly, alopecia-type tinea capitis, which I don't really consider to be pure kerion and which I wouldn't use prednisone on and don't think should be excluded. So I mean I think, in real life, the very pure kerion probably represents--I don't know--in my experience--I'd be interested in what others have seen, but probably 1 to 2 percent of what we see, absolute, pure kerion. But there are these other kids who have boggy, tender areas, but it's in a field of sort of more ordinary tinea capitis.

DR. McGUIRE: I think that a lot of people would call those kerions. I mean, I think we're going to confuse things if we try to eliminate that.

Madeleine, did you have a comment?

DR. DUVIC: A quick comment. I would say that one end of the spectrum is kerion where it's mainly host response that's very brisk against the fungus. The fungus isn't different, but it's the host reacting to the fungus that causes the scarring and the inflammation. The other end of that spectrum is the carrier state where you have no reaction to the fungus by the host at all, not any kind. What you're describing is in between.

DR. McGUIRE: Dr. Friedlander, where are we with this?

DR. FALLON-FRIEDLANDER: I think it will be important to identify it as a subset, perhaps, because most

of us--please, everyone pipe in if you don't agree--recognize that it takes a little bit longer often for the kerions to resolve, so that if we were to bias one group with more kerions than not, that would bias results of any study. So if we include the kerions, I think your idea of making it a separately identifiable group is extremely important.

DR. McGUIRE: Jon, are you comfortable with that?

DR. WILKIN: Yes. Actually, I think I heard several options. One option would be that whatever the clinician calls kerion that would require corticosteroids, in their opinion, that patient would not be in the trial. And then kerion which doesn't, or which--let me say that again. Kerion which doesn't require additional corticosteroids, those patients can be in the trial. If it requires additional corticosteroids, they could be excluded.

An alternative to that is everyone who enters the trial with any of these varieties and has some touch of kerion, either the big boggy or the little intermittent areas of somewhat bogginess, they could be stratified. That would be another way to approach it.

DR. McGUIRE: That would be my choice because the threshold for treating with steroids in the face of a kerion is very different. I suspect Ilona's threshold is here. Mine is a little lower. I don't know where Paul's is, but

it's--

DR. HONIG: Where's mine?

DR. McGUIRE: I don't know.

DR. HONIG: It's way low.

DR. FRIEDEN: It's way high.

DR. HONIG: No, it's way low.

DR. FRIEDEN: Your threshold.

DR. McGUIRE: All right, your threshold, okay.

DR. FRIEDEN: It's high.

DR. HONIG: Oh, it's high.

DR. FRIEDEN: Threshold.

DR. HONIG: It's high; it's very high.

DR. McGUIRE: That's what I mean.

DR. HONIG: Yes.

DR. McGUIRE: There would be misinterpretations, okay.

DR. FRIEDEN: I think one thing there was consensus about in the discussions outside of the immediate discussion, however--I guess Raza is gone, but this concept that you have to have a black dot in order to enroll in a study seems wrong to us as clinicians.

DR. McGUIRE: We've already dealt with that, I believe.

DR. FRIEDEN: Okay.

DR. McGUIRE: Which dermatophytes should be

included and to what extent?

Well, we can--okay, Dr. Friedlander

DR. FALLON-FRIEDLANDER: There is a sense among most of us pediatric dermatologists in the room that Microsporum canis may not respond in the same way that Trichophyton tonsurans does. And I'm curious how the group feels about do we just mix all that data together or not.

DR. McGUIRE: I think the organism has to be--I think they have to be identified according to organism

DR. FALLON-FRIEDLANDER: Stratified, agree. If you're going to do it, you have to identify--again, it's like the kerion issue, if we're going to include it. And some people would rather just look at the Trichophyton response.

DR. HONIG: Let's do them all.

DR. McGUIRE: Well, operationally, it's going to be 95-percent tonsurans, but we shouldn't exclude others if there's a worthy population.

Who am I missing?

DR. TSCHEN: Furthermore, I think they will be enrolled in the study because you will not know the result of the culture until two, three, four weeks after they start the drug. So I guess that will be clarified at the end of the study.

DR. DUVIC: It seems like you need to know whether

canis is as responsive and if you don't include them, you won't get that information.

DR. McGUIRE: Okay, agreed

DR. FALLON-FRIEDLANDER: As long as they're identified as a separate group.

DR. McGUIRE: Dr. Elewski?

DR. ELEWSKI: You could probably get a bedside diagnosis of M. canis by fluorescing the patient initially and if it fluoresces, it's M. canis, and if it doesn't fluoresce, it's probably T. tonsurans.

DR. McGUIRE: You know, there are some dermatologists out there who don't use the Wood's lamp anymore.

How is the diagnosis best established? I think we've dealt with that.

DR. WILKIN: Excuse me, Dr. McGuire.

DR. McGUIRE: Dr. Wilkin?

DR. WILKIN: If I could ask just one more question about the T. tonsurans, how about T. tonsurans from overseas? I'm not sure if it exists that much overseas, but would we be able to extrapolate into the United States and is it the same subtype? I think you mentioned there might be three or four subtypes.

DR. BABEL: I think even within the United States we're going to see strain varieties of Trichophyton

tonsurans. And worldwide, the variety selferium is felt to be maybe a little bit more aggressive than the other strains, but it's not unique to any geographic location. So I don't think that's a concern, quite honestly.

DR. McGUIRE: How is the diagnosis best established? I think we decided that KOH was not a sufficiently good test; that we would depend upon culture. And the culture technique--I still use a toothbrush, but it sounds like other people are using swabs and blades.

DR. FRIEDEN: Would a positive KOH be an acceptable entry criteria without a culture? I mean, I'm not clear on that because depending on whose hands it's in--

DR. McGUIRE: Unless it were mine.

DR. FRIEDEN: And then the question is do we have to have the culture before we start treatment. Before you enroll the patient, do you have to have that positive culture?

DR. McGUIRE: Okay. Let's deal with that with a separate--

DR. FRIEDEN: Well, that's how you establish diagnosis.

DR. McGUIRE: Yes.

DR. FRIEDEN: Yes.

DR. McGUIRE: But I would--let's deal with that in just a minute.

DR. FRIEDEN: Okay.

DR. McGUIRE: Any other comments on establishing diagnosis?

DR. TSCHEN: I don't think the KOH should be excluded. I think it should be part of the protocol, and I think you expect that most of the investigators who are going to be--all of the ones who are in here probably can read a KOH fairly well, you know. So I think it is important to have it in there, even though you are not relying as a gold standard.

DR. McGUIRE: Would you accept a KOH without the culture?

DR. TSCHEN: Yes. If any in this room does it, yes.

DR. McGUIRE: Dr. Elewski?

DR. ELEWSKI: I think a KOH from the skin is easy to do, from the nail is easy to do, but from the hair is tough and even the best dermatologist will mess it up.

DR. McGUIRE: That makes me feel a lot better.

DR. ELEWSKI: So I think that a KOH alone is not sufficient because it could be falsely positive or negative.

DR. McGUIRE: I agree.

DR. TSCHEN: But I don't think it should be excluded. That's my point.

DR. McGUIRE: No one is excluding it, but there's

some reluctance to accept it--

DR. TSCHEN: Oh, I agree.

DR. McGUIRE: --as the diagnosis.

DR. TSCHEN: As the only one, yes.

DR. FALLON-FRIEDLANDER: There's also a technical part to that which is that cultures are very easy to do from swabs. I don't feel as comfortable doing a KOH from a swab and if we start to pluck and scrape, I think that that decreases the compliance, the return rate on the patients, because it becomes more traumatic for them to go through the process. So, that's another part of the issue. And, again, looking through studies, that's a big problem. Not only did it take so long for the patients to be followed, but I think if there's any trauma involved, they don't want to come back.

DR. McGUIRE: Dr. Wilkin, we're adding a question to your group of six, and that is if a child is seen who clinically has a diagnosis of tinea capitis, should treatment begin before the culture is returned. Operationally, that's what happens. The child is treated and then if the culture were negative and you were still convinced that the child had tinea capitis, you'd probably do another culture or you'd see if the laboratory was having a bad week or you'd find out if the mycocell or the DTM was no good. But I would suggest that any study like this be

started on clinical grounds and then if you needed to drop individuals from the study on the basis of negative cultures that be allowed.

Dr. Wilkin?

DR. WILKIN: That actually is the routine in our division and after excluding the people who ended up with a negative culture at the beginning of the trial, we're left with the residue of what we call the modified intent to treat population. And so that's the group that we would look at for efficacy.

DR. McGUIRE: Question 4: How and when is cure best established? How long should the patient-subjects be followed after discontinuation of treatment? There are some real practical problems in number 4.

Paul?

DR. HONIG: This is probably the hardest one to answer. I would say that regrowth of hair is not necessary. I would say that signs of inflammation, scaling and erythema should be gone, and I think you need to follow out probably for 12 weeks.

DR. McGUIRE: Twelve weeks after discontinuing therapy or from beginning?

DR. HONIG: No, probably from beginning of therapy.

DR. McGUIRE: Are you going to do repeat cultures?

DR. HONIG: Each time we see the patient.

DR. McGUIRE: Okay, so 12 weeks from inception, with repeat cultures. From a practical standpoint, if you make the clinical diagnosis of tinea capitis, obtain a culture, initiative therapy, when do you see that patient again? This is not a study patient; this is a patient you're taking of in your office.

DR. FRIEDEN: Monthly is what I do; monthly.

DR. McGUIRE: Okay.

DR. HONIG: Monthly.

DR. McGUIRE: Monthly, monthly, monthly, six weeks, okay.

DR. FRIEDEN: Can I add something to what Paul said? I think that we need to look at signs and symptoms. So I think there needs to be a symptom component as well as a sign component to the improvement because I think, like you've said, parents do know when these kids are getting better and they will see them with unadulterated scalp before the pomades get put on. I often ask them, I say, please don't put on any pomade for two to three days before you come in. But, often, they do and so they can tell you something about what the state of the scalp is. You may not be able to see that scale even if it's still there.

DR. McGUIRE: Okay. Jon, are you getting what you need on 4?

DR. WILKIN: Very helpful. Thank you.

DR. McGUIRE: Okay, number 5. Dr. Elewski, I'm going to give that one to you.

DR. MILLER: Can I ask a question?

DR. McGUIRE: Yes, Fred.

DR. MILLER: This is a question about the cultures. You know, we talked about the carrier state and all those variables, but if you have a child who's healing and you've treated for the six weeks, is it really necessary to reculture at that point if there is no recurrence or relapse, or whatever word you want to use? I'm thinking about cost. I mean, you've treated. The child is getting better. Is it necessary to reculture?

DR. McGUIRE: But you're in two modes here. One is doing a study to establish efficacy and the other is clinical care, and I think there would be a different standard for what the study would--

DR. MILLER: Okay, yes. I'm sorry.

DR. McGUIRE: Is that fair?

DR. HONIG: Yes.

DR. DUVIC: Can I ask a question?

DR. McGUIRE: Sure.

DR. DUVIC: If you treat to clearing clinically, but the culture is still positive, are they infected or are they just carriers now?

DR. HONIG: They're carriers as far as I'm concerned.

DR. DUVIC: They're carriers, okay, so--

DR. HONIG: Because if you--just from the information that you were given today, we could be treating for a very long time if you go by the culture. I mean, there are some--remember, we said there were some children that were positive eight months out. I'm not going to keep treating a child for eight months if we've got complete regrowth of hair and everything looks wonderful and they have a positive culture. I'm just not going to do it.

DR. DUVIC: But maybe you should be putting them on a shampoo or something.

DR. HONIG: Well, that's going to come. We're going to get to that, I assume.

DR. McGUIRE: We're gong to use the zinc parathion on them.

[Laughter.]

DR. McGUIRE: Fred?

DR. MILLER: Yes. I'm still not comfortable with this. If you culture and you get a positive at the end of the study, well, then the study would have to be set up so that you would do another culture down--even if you're not going to treat again, if they're clinically not involved, but further down the road you're going to want a culture to

see if the carrier state has been eliminated. Is that correct?

DR. HONIG: I think that's going to be tough if we use adjunctive therapy. I think that goes hand-in-hand.

DR. MILLER: Because in a study, if you end up with a positive culture after you've treated, what is the conclusion going to be, carrier or--

DR. HONIG: Right, I understand that. If we use adjunctive therapy, that will be taken care of. If we don't, then it's going to be interesting.

DR. McGUIRE: Dr. Elewski?

DR. ELEWSKI: Every study I reviewed used the criteria of negative culture as the endpoint and that's how they defined cure to clinical and also culture cure. So I think you have to do it just like you do other mycotic--you know, the nail. If the culture is negative, they're cured. If the clinical symptoms are resolved, they're cured. So you can look at both parameters.

DR. McGUIRE: Okay. For helping us out with that, you get question 5.

DR. ELEWSKI: Right. Placebo-controlled studies in tinea capitis, I think, are unethical. I don't think that should be done. I think you need an active comparison and griseofulvin should be an active comparison, I believe. It is the current standard. The big problem is what dose of

griseofulvin do you use. Do you use the dose recommended in the PDR, the 5 milligrams per pound per day, or do you use the higher dose? And I think you use the standard that everyone uses; 15 milligrams per kilogram per day is probably a good dose to use.

DR. McGUIRE: Does everyone concur? John concurs.

DR. DiGIOVANNA: I concur, but I have a question--

DR. McGUIRE: Okay.

DR. DiGIOVANNA: --that I've been holding for a while. Dr. Elewski showed some data on using Lamicil in a 7-day versus a 14-day--somewhat of a pulse treatment. And I'm not quite sure whether Lamicil resides in the hair shafts the same way that it resides in the nail. I would assume that it probably does to some degree.

When we treat dermatophyte infections, they're a little different than treating bacterial infections where you want to stamp out the last staph, and I think of them conceptually as conditions similar to a few others. For example, the way I like to look at tinea versicolor is if you're going to treat it systematically, there's lots of organism in the environment, there's lot of organisms on the patient and if I give him a two-pill treatment, I want to repeat that somewhere down the line maybe a few weeks later, maybe a month later, thinking that I will--maybe this is fantasy or intuition--a lot of the fomite-related material

for reinfection is decreased.

The same sort of concept is true when you treat scabies. I mean, you frequently will treat and there will be reinfection or there will be not exactly the last mite eliminated from where you want it to be eliminated. But if you treat it a second time around and they go through the whole thing twice, a lot of the same conceptual ideas occur.

And because of that, I would think that a short-term--that in designing these studies, rather than design them in the standard way we always do and then have the dermatologist figure out, in Europe we like to use pulse treatment once a month for three months or this sort of thing, that conceptually there might be more creative ways of designing them. So separating that two weeks of Lamicil with a one- or a two-week or whatever a reasonably thought-out time period would be, I would think would be one sort of a possible control that could be used in designing these therapies. And I just wanted to see what other people thought about that approach.

DR. McGUIRE: Well, let's see what Dr. Elewski says.

DR. ELEWSKI: Well, actually, Dr. Gupta did that with itraconazole and he did two studies and gave 15 patients one pulse, one week, of treatment, waited two weeks. And then those that required another week got a

second week and those that didn't, didn't, and, if necessary, a third pulse. And he found 3 weeks of active therapy, with 2-week vacations between these weeks of therapies, was effective for all 15 of his patients.

I'm not aware of a pulse study of--there is a pulse--

DR. FALLON-FRIEDLANDER: Yes. Gupta also did a pulse study on terbinafine, again small numbers, but showed the same thing, very high cure rates with pulsing.

DR. ELEWSKI: The problem is we don't have the pharmacokinetic data in the hair.

DR. DiGIOVANNA: Yes, but what I'm saying is, is three weeks given with intervals much better than three weeks given at one time?

DR. FALLON-FRIEDLANDER: Many of us think it would be the case from the pharmacokinetics that we have in nails and in skin. And I think there's some small data on beards, definitely for itraconazole for beard hair, where they showed the same kind of compartmentalization. So there's a reservoir effect. So many of us do feel that's the way to go.

Now, the devil's advocate group has said to us, you're never going to get a family to be compliant that way where you tell them to come in for one week, take it, and then they have to see you two weeks later and take it again.

That's the argument that has been leveled when I have proposed this, and many of us have talked about pulsing as intuitively being more sensible for a drug with a long half-life in the tissue where you're looking.

DR. DiGIOVANNA: But in a study, you don't have to do that. In a study, you could have placebo pills throughout the non-pulsed time. I mean, everybody takes one pill. There are many ways to get around it. My real question is, is this something to convince the pharmaceutical industry or to convince the agency, or for the agency to tell the pharmaceutical industry they'd be willing to hear? I guess I wanted the experts to say that this is something that probably would add to the efficacy, and if so should pursued.

DR. FALLON-FRIEDLANDER: I agree with you and have discussed it. I don't know whether Paul and Ilona--how do you feel about pulsing?

DR. FRIEDEN: I think that there's a lot of merit to the concept. I'm more concerned that we get some study off the ground to just even do conventional dosing, and if we can get a large enough study to do both, that would be ideal, obviously. But if we had to choose only one method of doing it, I would probably start with conventional dosing. If we could do two arms, plus a griseofulvin arm, then I think it would be fantastic.

DR. McGUIRE: But the small amount of data available at the present on pulse therapy is very promising, and that may be where we are in a year or two years.

Dr. Aly, did you want to comment?

DR. ALY: I think we are comparing here two different types of diseases, like scabies and tinea versicolor or pityriasis versicolor. They are entirely two different diseases. Scabies is exogenously acquired and versicolor is endogenously acquired as part of the resident flora. So you really cannot compare those diseases together.

Similarly, when we talk about onychomycosis or tinea corporis, as Bonnie mentioned, those are again very different diseases from tinea capitis because in tinea capitis we do have a carrier state and we usually don't have a carrier state once you treat tinea corporis and tinea ungum.

DR. McGUIRE: I would like--oh, yes, come to the microphone.

DR. SCHRODE: Kathy Schrode, Bristol Meyers Squibb. One of the issues you've raised about pulse dosing is having patient on drug and off drug. Very applicable to that certainly in the study situation is using blister packs with day number one, two, three. You can have active and then placebo packaged all in one package. The patient comes

back in a month.

DR. DUVIC: In children, though, you need liquids.

DR. McGUIRE: I don't think you heard the rejoinder.

DR. DUVIC: I'm sorry. I think I heard from the pediatricians this morning that in children the optimal formulation would be a liquid, so that makes blister packs a little bit more difficult unless they're chewable tablets that taste great.

DR. FALLON-FRIEDLANDER: But we don't have a liquid to test, other than fluconazole. We don't have a liquid anyway right now for itra or terbinafine that we could use.

DR. McGUIRE: Dr. DiGiovanna?

DR. DiGIOVANNA: I don't have kids. It's been a long time since I've been a kid, but I vaguely remember--and people are very creative with these things. I vaguely remember some candy as a liquid that came in a little thing. You popped the top off and it was a one-dose thing, and I'm sure that a blister pack or a daily dose of a liquid could be created with some delivery systems.

DR. McGUIRE: That was a Fentanyl lollipop, I think, John.

[Laughter.]

DR. McGUIRE: Dr. Honig, number 6 is yours. Is

adjunctive treatment with a topical agent of patient-subjects necessary or appropriate? Is treatment with a topical agent necessary or appropriate for either culture-negative for culture-positive, asymptomatic family carriers? You can deal with that second part separately.

DR. HONIG: I can only tell you my gut feeling because I don't think there are studies out there that definitively answer one way or another whether adjunctive therapy is that much better, because if you look at the 1- and 2.5-percent study, they didn't get negative cultures until 4 weeks. We had 15, 16 patients that were negative in 2 weeks, very small numbers. My gut feeling would be that you should start shampooing, mainly because of the fact that I would like to get those cultures to be negative when the clinical findings are improved.

DR. McGUIRE: Well, this bears on clinical practice. I have children shampoo, but I do it because I think I'm reducing their infectivity to the other kids.

DR. HONIG: Yes; oh, yes. Well, that's what I think that we're doing, too.

DR. McGUIRE: And that's sort of a sub-theme in this.

DR. HONIG: Yes, and I think that's going to be important for getting them back to school.

DR. McGUIRE: Yes.

DR. HONIG: And it'll be important even within their own household.

DR. McGUIRE: Do you keep your kids out of school once you initiate therapy?

DR. HONIG: No, no.

DR. FALLON-FRIEDLANDER: So you're saying in the study design you're going to use topical therapy?

DR. HONIG: Yes.

DR. McGUIRE: Is treatment with a topical agent necessary or appropriate for either culture-negative or culture-positive, asymptomatic family members?

DR. DiGIOVANNA: Joe, may I ask one question?

DR. McGUIRE: Sure.

DR. DiGIOVANNA: I'm sure you said this and I'm sure I missed it and I apologize before. But except for the cultures, is there a difference in the cure rate? I remember that study that you showed--

DR. HONIG: No difference in cure rate when you use adjunctive therapy. We thought at first that you could cure tinea capitis with just using the shampoo. We didn't publish that part.

DR. DiGIOVANNA: What would happen if you were pharmaceutical company "x" and you wanted to design a clinical trial for your product and had to include an adjunctive agent with that? That would probably be required

in the labeling, but it might not necessarily increase the cure rate. It might only increase the culture negativity rate. Isn't that possible from what we know from the data?

DR. HONIG: That is possible, but again I don't go by the culture. I go by what I see clinically as a way of deciding when to stop treatment because in many of these children you could go on and on and on with positive cultures, and then what have you accomplished?

DR. McGUIRE: Dr. Wilkin, first, let me thank you for putting the symposium together.

Eva? I'm sorry.

DR. SIMMONS-O'BRIEN: I just wanted to make a few comments. One, I wanted to ask a question to our expert panel in terms of the shampooing issue, since you've stated that it is difficult for your patients to comply with that. Is the option available to use the selenium sulfide as a first shampooing and then be able to still have efficacy of the selenium sulfide and use after that a more conditioning shampoo, followed by a conditioner, or will that negate the effect of the selenium sulfide? Do you know that?

DR. HONIG: No idea.

DR. SIMMONS-O'BRIEN: Okay. Well, just in terms of giving the families an option, and also in the studies, is it ever possible to allow for an allowance, an actual monetary allowance, because I think probably a lot comes

down to cost and time in terms of frequency of hair wash? I don't think it's that the majority of these parents want their children to go for long periods of time without having their hair washed. I think a lot of it boils down to cost and to time, and that's what ends up happening.

And then I'd like to--kind of a swift-in digression, but I think Jonathan was relevant in many of his digressions. I would just caution the use of generalities of African American and African American children. I think many of the--from what I've heard, the children who have been studied, it sounds like they share commonalities, in that they're in urban environments. And I'm even going to assume that maybe they're of lower-income status. Maybe there are commonalities in terms of grooming techniques, maybe commonalities in skin types and in actual structural component of hair shafts.

But African Americans in this country are one of the most heterogenous groups of individuals around, ranging from skin types 2 to 6, poker-straight hair as silky as any caucasian's may be, to very coarse, kinky hair. So I think that it's important to qualify, and then as an investigator to look to see why there is an increased incidence or prevalence in a group. What are the commonalities? And it might be interested to go to some--if you think it is something unique amongst African Americans, to go to some

organizations that have higher-income groups or members, as in Jack and Jill Links. Go to Oak Bluffs in Martha's Vineyard in the summertime, look at that group of children and see is it something that also is common or prevalent, because I think we have a responsibility to be, still in 1998, very sensitive and politically aware. And things trickle down from us and the last thing we want is a sound bite in Time magazine, in the medical report, "endemic in black children." That's dangerous.

DR. McGUIRE: Eva, I'm glad you said that and you said it, I guess, probably better than anybody else. And it needs to be on the record and I think Dr. Wilkin heard it.

DR. HONIG: I agree with you. I think that I have a higher-income group of people that I see, as well as the indigent, and I see in the higher-income group of black and white patients--I don't see tinea capitis very often in that group. I see it mainly in the indigents.

DR. McGUIRE: I started off to thank the people who have given us their time today--Dr. Frieden, Dr. Fallon-Friedlander, Dr. Babel, Dr. Elewski, Paul Honig. And I especially would like to thank Jon Wilkin for putting together an educational symposium. I learned a lot from it and I'd like to thank the members of the Advisory Committee. And someplace I have written that we need to catch a bus at 7:00 a.m. tomorrow morning to go out to Fishers Lane.

Jon, do you have any last words? I'm sorry. Jon, say your last words. That's what I wanted to say.

[Laughter.]

DR. WILKIN: You deconstructed even that, Joe. That's great. Well, those of us at the FDA learned a lot from the experts and from the discussion today, the comments made by the Committee members. And this will materially impact and improve our thinking about these clinical trial designs for tinea capitis.

Thank you.

DR. McGUIRE: We are adjourned. See you in the morning.

[Whereupon, at 4:32 p.m., the meeting of the Advisory Committee was adjourned.]

CERTIFICATE

I, **VICTORIA RANUCCI,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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